

Systematic Review

Efficacy and Safety of Plasma Rich in Growth Factors Intra-Articular Infiltrations in the Treatment of Knee Osteoarthritis

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Purpose: The goal of this study was to systematically review the efficacy and safety of plasma rich in growth factors (PRGF) as a treatment for reducing symptoms in patients with knee osteoarthritis. **Methods:** A comprehensive and systematic literature search was conducted for PRGF treatment of knee osteoarthritis following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. All the studies had to include a PRGF group and a control group. Pre- and post-treatment measures of joint pain, reduced function, and stiffness were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index, Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee score, Lequesne index, or number of Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI) responders, with a follow-up period of at least 4 weeks. An assessment of both the quality and risk of bias of the studies was conducted. **Results:** The literature search yielded 91 citations, but only 5 were eligible publications that met the inclusion criteria (2 randomized controlled trials, 2 prospective studies, and 1 retrospective analysis). Two studies were rated as having a low risk of bias whereas 3 had a high risk. In both randomized controlled trials, it was observed that after 6 months of treatment, the number of patients with a pain reduction of more than 50% was significantly higher in the PRGF group. In 2 other studies, the patients treated with PRGF showed a significant pain reduction compared with the control group. The remaining variables (Western Ontario and McMaster Universities Osteoarthritis Index scale for pain, function, and stiffness; Lequesne index; Knee Injury and Osteoarthritis Outcome Score scale; and number of OMERACT-OARSI responders) showed a statistically significant superiority of the group treated with PRGF. **Conclusions:** The current clinical evidence suggests that PRGF intra-articular infiltrations in patients with knee osteoarthritis reduce pain and therefore are clinically efficacious in osteoarthritis treatment. **Level of Evidence:** Level III, systematic review of Level I, II, and III studies.

Osteoarthritis (OA) is a multifactorial polygenic degenerative disease that is mechanically induced, whose progression might be attributable to proinflammatory signaling molecules that overall leads to the synovial joint failure as organ, and for which pain represents the clinical hallmark of disease.¹⁻³ Although there is no consensus in defining and calculating knee OA prevalence, it is estimated that at least 10% of the

worldwide population aged older than 60 years may have symptoms of this condition,⁴ with a significant economic cost (>\$100 billion in the United States).⁵ Furthermore, the increase in both life expectancy and obesity will cause these values to increase significantly in the future.⁶

There are numerous preclinical studies, both in vitro and in vivo, supporting the clinical use of platelet-rich plasma (PRP) therapy in the treatment of articular pathology, including OA (as recently reviewed⁷⁻⁹). The rationale for the use of these types of biological therapies is based on the use of a mixture of autologous molecules in supraphysiological concentrations, with the purpose to influence and reverse the catabolic environment present in osteoarthritic disease and ultimately restore joint homeostasis.¹⁰ However, the different types of PRP available, which differ not only in composition but also in the way they are used, make it somewhat difficult to establish general rules about the efficacy and safety of these types of approaches.

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Plasma rich in growth factors (PRGF) is a 100% autologous PRP with a standardized composition and dosage. PRGF contains a moderated platelet concentration (2- to 2.5-fold increase compared with peripheral blood).¹¹ One of the most relevant and controversial issue is the presence of white blood cells (WBCs) in PRP. To distinctly define PRGF and thus be able to compare it with other PRPs, PRGF can be categorized according to the 3 classifications that have been proposed for PRPs. The first and most widely used classifies PRGF as pure PRP (P-PRP) because it does not contain WBCs.¹² The PRGF is classified as type 4-B (minimal WBCs, activated with calcium chloride, and platelet concentration below 5×) as proposed by other authors for sports medicine classification.¹³ Finally, PRGF would fit in the P2-x-B β category (platelet count greater than baseline levels to 750,000 platelets/ μ L, exogenous activation with calcium chloride, with WBCs—and specifically neutrophils—below or equal to baseline levels) according to the PAW (platelets, activation, and WBCs) classification.¹⁴

The purpose of this systematic review is analyze the scientific literature in depth to verify whether the intra-articular injection of PRGF, a specific PRP product, is safe and effective in the treatment of knee OA. In this way, this systematic review is expected to eliminate the variability present in other systematic reviews regarding the product used,^{15,16} thereby removing at least 1 confounding factor. To our knowledge, this is the first systematic review of the efficacy and safety of a specific platelet product (PRGF) in the treatment of OA of the knee.

Methods

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.^{17,18}

Eligibility Criteria

For assessment of PRGF treatment, only randomized controlled trials (RCTs) and comparative studies published in peer-reviewed journals or presented at scientific meetings (abstracts) were considered, including published comparative clinical studies, that examine the efficacy of intra-articular application of PRGF. Articles published until October 30, 2013, were reviewed.

Studies were included when participants were aged older than 18 years and had been diagnosed with OA of the knee according to the parameters proposed by the American College of Rheumatology.¹⁹

All studies had to include a PRGF treatment group and a control group (hyaluronic acid [HA], placebo, or another PRP). In addition, those studies that included the administration of concomitant treatments were included, provided that they had been controlled and distributed in a homogeneous fashion for both groups.

Studies that used PRP obtained by different methods from that used for PRGF¹¹ (Endoret; BTI Biotechnology

Institute, Vitoria-Gasteiz, Spain) were excluded, such as methods using double centrifugation, platelet activation by bovine thrombin, or platelet lysates, among others.

Search Strategy

For identification of the studies analyzed in this review, electronic searches of the following databases were performed: Medline PubMed, Ovid, Embase, PASCAL, and Cochrane Central Register of Controlled Trials. The search strategy was as follows: (PRGF OR plasma rich growth factors OR autologous growth factors OR platelet rich plasma) AND (knee osteoarthritis). Narrative reviews and editorials were also examined for references of potential trials. In the study selection process, 2 investigators reviewed the abstracts of potentially eligible articles.

The full text of the selected articles was reviewed again by the same authors, and only those articles that met the inclusion criteria previously described were included in this review. Those items potentially including redundant information (same results published in different publications) were analyzed to confirm that the results were original. A complete flow diagram to indicate the flow of information during article selection was created following the PRISMA guidelines.¹⁸

Outcome Measures

Eligible studies had to include at least 1 of the following variables measured on a validated scale: joint pain, function, and stiffness. Studies that evaluated different scales (Western Ontario and McMaster Universities Osteoarthritis Index or Lequesne index) were also included. The outcome variables could include other variables or factors that were unadjusted or adjusted. We also included variables generated from the initial variables (pain, function, and stiffness) after comparing the initial and final results of the same. In addition, follow-up time for treatment/intervention trials had to be a minimum of 4 weeks.

Adverse events described in the different studies were screened. We observed whether minor or significant adverse events were described, as well as whether they predominated in the PRGF-treated group or control group.

Initial Quality Assessment

The data analyzed for each study to assess the quality of the included studies were as follows: (1) study methods (treatment allocation, blinding, number of patients lost or excluded after randomization); (2) participants (demographic and clinical characteristics of patients included, recruiting methods, sample size, patient age, patient gender, inclusion/exclusion criteria); (3) experimental intervention (type, dose, and frequency of application of treatments, time of follow-up);

and (4) control (type, dose, and frequency of application, time of follow-up, variables analyzed).

To determine the risk of bias of the included studies, the Review Manager program (RevMan, version 5.2 [2012]; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used. A form including the following sections was filled out: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding (performance bias and detection bias), (4) incomplete outcome data (attrition bias), (5) selective reporting (reporting bias), and (6) other bias.

The overall risk of bias in any of the included studies was categorized according to The Cochrane Collaboration's tool for assessing risk of bias in randomized trials²⁰:

- Low risk of bias (reasonable bias unlikely to seriously alter the results) if all key domains were assessed as having a low risk of bias
- Unclear risk of bias (reasonable bias that raises some doubt about the results) if 1 or more key domains was assessed as having an unclear risk of bias
- High risk of bias (reasonable bias that seriously weakens confidence in the results) if 1 or more key domains was assessed as having a high risk of bias

Data Extraction and Analysis

Outcomes were categorized by type, and for each outcome, the median or mean values (\pm standard deviation) were extracted when possible. Data were imported into the RevMan program to calculate 95% confidence intervals and *P* values using fixed-effect models where possible. Dichotomous variables were expressed by determination of absolute and relative frequencies. Quantitative variables were summarized using the mean and standard deviation. The measure of effect was made by determining the relative risk or odds ratio with its respective 95% confidence interval in the case of dichotomous variables. For quantitative variables, we calculated the mean difference with confidence intervals at 95%.

Unit-of-Analysis Issues

The Mantel-Haenszel method was used with risk difference as the effect measure in the case of dichotomous events, and the inverse variance method was used with the weighted mean difference as the effect measure in the case of continuous (interval) data.

Grading

After data were extracted and initial quality assessment was complete, important and critical outcomes were agreed on using consensus and quality assessment. The summary of findings for studies comparing the infiltration of PRGF versus control was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system^{21,22} for grading

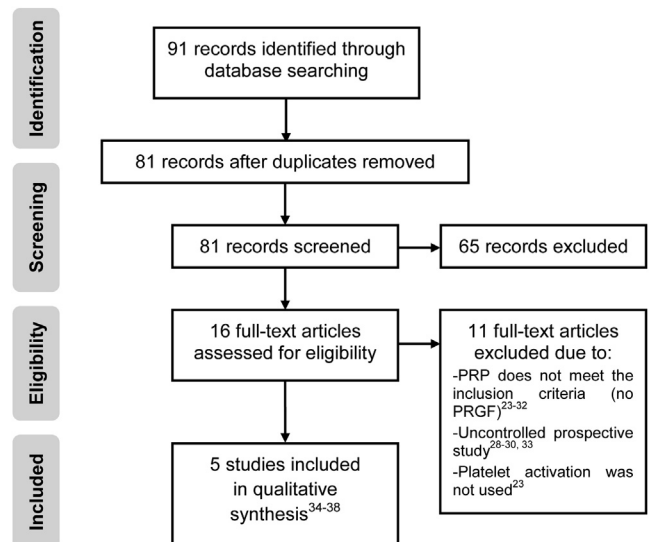


Fig 1. Flow diagram of study selection showing process of identifying and selecting relevant studies included in systematic review.

each outcome by use of GRADEpro software (version 3.6; McMaster University, Jan Brozek, Andrew Oxman, Holger Schünemann, Hamilton, Ontario, Canada).

Results

Study Selection

The protocol search terms resulted in 91 citations (Fig 1). Initially, we proceeded to eliminate 10 duplicate records. Subsequently, 65 studies were excluded for 1 or more of the following reasons: narrative reviews, noncomparative studies and/or case series, studies confounded with other treatments, or reporting of insufficient outcome data. Potentially eligible studies ($n = 16$) were identified per protocol criteria, and the full text was screened. Of these studies, 11 were excluded because they did not meet the protocol eligibility criteria (no PRGF was used,²³⁻³² uncontrolled prospective studies were conducted,^{28-30,33} and/or controlled platelet activation was not performed²³). Therefore 5 studies were included in this systematic review³⁴⁻³⁸ (Fig 1).

Study Characteristics

Eligible publications were published between 2008 and 2013 in international peer-reviewed journals. The 5 studies included a total population of 530 patients. Of the selected studies, 2 were classified as RCTs,^{36,38} 2 were prospective studies,^{34,37} and 1 was a retrospective analysis.³⁵ Table 1 describes the characteristics of the 5 studies included in the systematic review.

Risk of Bias of Included Studies

A summary of the risk-of-bias assessment is shown in Fig 2. Two studies were described as randomized, and

Table 1. Characteristics of Studies Included in Systematic Review

Study	Design	Participants and Inclusion and Exclusion Criteria	Interventions	Outcomes	Follow-Up
Sánchez et al., ³⁵ 2008	Retrospective observational study Open blind Single center	No. of patients: 60 Country: Spain Mean age: PRGF, 63.5 yr; HA, 60.9 yr % female: PRGF, 66%; HA, 60% Inclusion criteria: patients with knee OA diagnosed according to American College of Rheumatology criteria Patients in both groups were matched by age, gender, and BMI and by radiographic severity (same Ahlbäck grade). Radiographic severity was assessed by anteroposterior weight-bearing radiographs scored according to Ahlbäck grade. Idiopathic and secondary post-traumatic and mechanical OA was included. Exclusion criteria: OA due to joint inflammatory disease and other diseases affecting knee; generalized OA or arthroscopic lavage in year before treatment; or intra-articular treatment within previous 3 mo	PRGF v HA 3 intra-articular injections (8 mL) on weekly basis Both treatments administered at 1-wk intervals	Patients with 40% decrease in WOMAC pain score	5 wk
Filardo et al., ³⁴ 2012	Observational study (cohort study) Open blind Multicenter	No. of patients: 144 Country: Italy Mean age: PRGF, 53.8 yr; PRP, 50.3 yr % female: PRGF, 20%; PRP, 29% Inclusion criteria: patients affected by chronic (≥ 4 mo) pain or swelling of knee and imaging findings (radiograph or MRI) of degenerative changes of joint Patients were divided into 3 categories: degenerative chondral lesion (Kellgren-Lawrence grade 0), early OA (Kellgren-Lawrence grade I-III), or advanced OA (Kellgren-Lawrence grade IV). Exclusion criteria: systemic disorders or immunodepression; patients receiving therapy with anticoagulants-antiaggregants; use of NSAIDs in 5 d before blood donation; or Hb values <11 g/dL and platelet values $<150,000/\text{mm}^3$	3 injections of platelet concentrate prepared with single-spinning procedure (PRGF-Endoret) v 3 injections of PRP obtained with double-spinning approach Administration every 3 wk	IKDC	6 mo
Sánchez et al., ³⁶ 2012	RCT Double blind Multicenter	No. of patients: 176 Country: Spain Mean age: PRGF, 60.5 yr; HA, 58.9 yr % female: both groups, 52% Inclusion criteria: male and female patients aged between 40 and 72 yr; diagnosis of tibiofemoral OA of knee by radiography; joint pain >35 mm on 0- to 100-mm VAS; radiologic severity grade <4 according to Ahlbäck grade; BMI ranging between 20 and 32; and possibility for observation during follow-up period Exclusion criteria: bilateral knee OA requiring infiltration in both knees; BMI <33 ; polyarticular disease; severe mechanical deformity; arthroscopy within past year; HA intra-articular infiltration within past 6 mo; systemic autoimmune rheumatoid disease (connective tissue disease and systemic necrotizing vasculitis); glycosylated Hb $>7\%$; blood disorders (thrombopathy, thrombocytopenia, anemia with Hb <9 g/dL); patients undergoing immunosuppressive therapy and/or warfarin therapy; treatment with steroids during 3 mo before inclusion in study; or treatment with NSAIDs during 15 d before inclusion in study	PRGF v HA (Euflexxa, Ferring Pharmaceuticals, Copenhagen, Denmark) 3 intra-articular injections on weekly basis	Patients with 50% decrease in WOMAC pain score OMERACT-OARSI responders WOMAC pain score WOMAC stiffness score WOMAC function score Lequesne index	6 mo

(continued)

Table 1. Continued

Study	Design	Participants and Inclusion and Exclusion Criteria	Interventions	Outcomes	Follow-Up
Vaquerizo et al., ³⁸ 2013	RCT Single blind Single center	No. of patients: 60 Country: Spain Mean age: PRGF, 62.4 yr; HA, 64.8 yr % female: PRGF, 66.7%; HA, 54.2% Inclusion criteria: age >50 yr; clinical symptoms >6 mo; Kellgren-Lawrence grades II-IV; and no NSAID or steroid treatment in past 3 mo Exclusion criteria: intra-articular HA injection in past 6 mo; severe mechanical deformity; allergic or sensitive to HA-based product; Dicoumarin (Novartis Farma, Naples, Italy) treatment that could not be reversed temporarily; polyarticular or infectious disease; systemic autoimmune rheumatic disease; blood dyscrasia; immunosuppressive or immunodepressive disease; BMI >40; or cancer/malignant lesions	PRGF v HA (Durolane, Q-Med AB, Uppsala, Sweden) PRGF: 3 intra-articular injections (8 mL) on weekly basis HA: single intra-articular injection	Patients with 50% decrease in WOMAC pain score OMERACT-OARSI responders WOMAC pain score WOMAC stiffness score WOMAC function score Lequesne index KOOS VAS for pain	6 mo
Say et al., ³⁷ 2013	Prospective study Open blind Single center	No. of patients: 90 Country: Turkey Mean age: PRGF, 55.2 yr; HA, 56.2 yr % female: 97.7% Inclusion criteria: bilateral gonarthrosis Exclusion criteria: any systemic disease; active tumor or hematologically malignant disease; infection; history of anticoagulant use; Hb value <11 g/dL; thrombocyte count <150,000/mm ³ ; or gonarthrosis radiologically with Kellgren-Lawrence grade IV	PRGF v HA PRGF: 1 intra-articular injection (8 mL) on weekly basis HA: 3 single intra-articular injections once a week		6 mo

BMI, body mass index; Hb, hemoglobin; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

adequate randomization was also described.^{36,38} Two trials were not randomized and were open label.^{34,37} and the other study was a retrospective comparative study.³⁵ From this assessment, 2 studies were rated as having a low risk of bias^{36,38} and the other 3 were classified as having a high risk of bias.^{34,35,37}

Grading

The quality of evidence for each outcome was determined. [Table 2](#) summarizes the findings for each variable. As can be observed by the 4-point scale (high, moderate, low, and very low) and individually for each trial, 13 of 17 outcomes had high quality (further research is unlikely to change the confidence in the estimate of effect) whereas 4 had low quality (further research is very likely to have an important impact on the confidence).

Effects of Intervention

[Figures 3 to 5](#) summarize the findings with respect to the main outcomes measured. The improvement in pain was analyzed as the primary outcome in 4 of the

	Filardo, 2012	Sanchez, 2008	Sanchez, 2012	Say 2013	Vaquerizo, 2013
Random sequence generation (selection bias)	+	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+	+
Blinding of participants and personnel (performance bias)	+	+	+	+	+
Blinding of outcome assessment (detection bias)	+	+	+	+	+
Incomplete outcome data (attrition bias)	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+
Other bias	+	+	+	+	+

Fig 2. Methodologic quality of studies included in systematic review. The risk-of-bias summary is shown for each study.

Table 2. Quality Assessment of Included Studies Using GRADE Approach

Study	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	No. of Patients	Quality	Importance
50% decrease in WOMAC pain score (follow-up, 6 mo)								
Sánchez et al., ³⁶ 2012	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	176	++++ (high)	Critical
Vaquerizo et al., ³⁸ 2013	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Critical
40% decrease in WOMAC pain score (follow-up, 5 wk)								
Sánchez et al., ³⁵ 2008	Observational study	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	60	++ (low)	Critical
30% decrease in WOMAC pain score (follow-up 6 of mo)								
Vaquerizo et al., ³⁸ 2013	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Important
OMERACT-OARSI responders (follow-up, 6 mo)								
Sánchez et al., ³⁶ 2012	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	176	++++ (high)	Important
Vaquerizo et al., ³⁸ 2013	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Important
WOMAC pain score (% change from baseline) (mean follow-up, 6 mo)								
Sánchez et al., ³⁶ 2012	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	176	++++ (high)	Critical
Vaquerizo et al., ³⁸ 2013	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Critical
WOMAC stiffness score (% change from baseline) (mean follow-up, 6 mo)								
Sánchez et al., ³⁵ 2008	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Critical
Vaquerizo et al., ³⁸ 2013	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Critical
WOMAC function score (% change from baseline) (mean follow-up, 6 mo)								
Sánchez et al., ³⁶ 2012	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	176	++++ (high)	Important
Vaquerizo et al., ³⁸ 2013	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Important
Lequesne index (% change from baseline) (mean follow-up, 6 mo)								
Sánchez et al., ³⁶ 2012	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	176	++++ (high)	Important
Vaquerizo et al., ³⁸ 2013	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	60	++++ (high)	Important
IKDC (mean follow-up, 6 mo)								
Filardo et al., ³⁴ 2012	Observational study	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	144	++ (low)	Critical
KOOS scale (mean follow-up, 6 mo)								
Say et al., ³⁷ 2013	Observational study	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	90	++ (low)	Critical
VAS scale (mean follow-up, 6 mo)								
Say et al., ³⁷ 2013	Observational study	Serious	No serious inconsistency	No serious indirectness	No serious imprecision	90	++ (low)	Important

IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

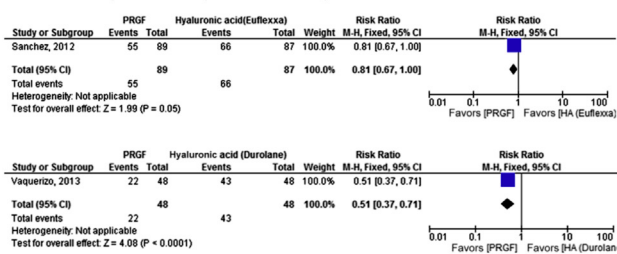
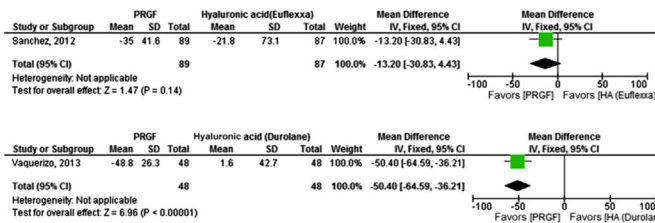
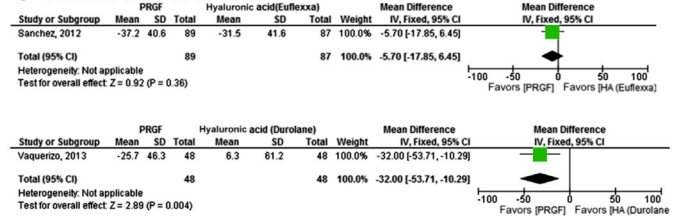
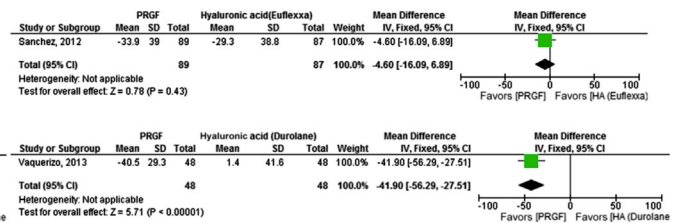
A WOMAC pain score (50% decrease)**B WOMAC pain scale****C WOMAC stiffness scale****D WOMAC function scale**

Fig 3. Forest plots created for Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) primary outcomes: (A) 50% pain score reduction, (B) pain scale, (C) stiffness scale, and (D) function scale. (CI, confidence interval; IV, inverse variance; M-H, Mantel-Haenszel.)

studies included in the review.³⁵⁻³⁸ It was observed in 2 randomized clinical trials that after 6 months of treatment, the number of patients with a pain reduction of more than 50% was significantly higher in the group treated with PRGF than in the control group (HA).^{36,38} In the RCT conducted by Vaquerizo et al.,³⁸ it was

noted that the rate of reduction in pain of more than 30% was significantly higher in the group treated with PRGF than in the control group (HA).

The retrospective study showed that the number of patients achieving an improvement in the pain variable (>40% decrease) was significantly higher in the group

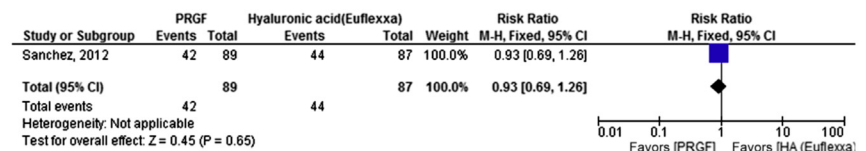
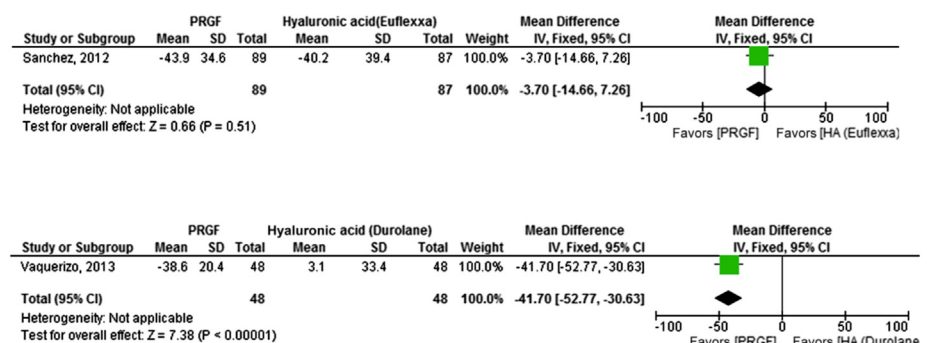
A OMERAT OARSİ responders

Fig 4. Forest plots for (A) OMERACT-OARSİ responders and (B) Lequesne index (CI, confidence interval; IV, inverse variance; M-H, Mantel-Haenszel.)

B Lequesne index

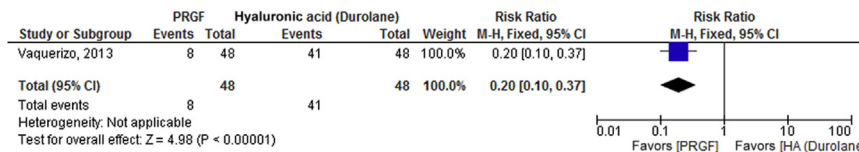
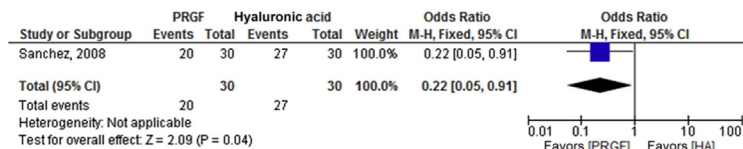
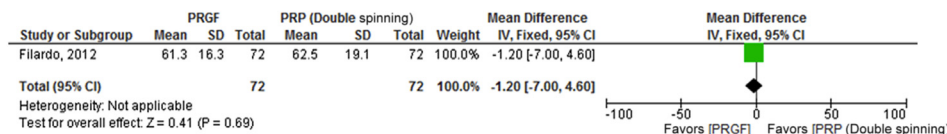
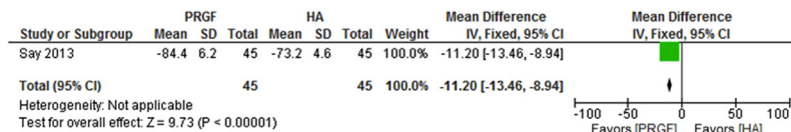
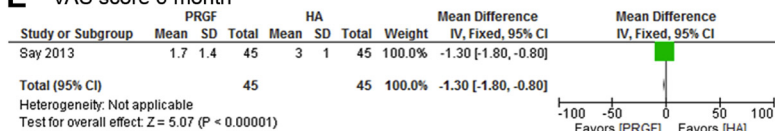
A WOMAC pain score (30% decrease)**B** WOMAC pain score (40% decrease)**C** IKDC score 6 month**D** KOOS score 6 month**E** VAS score 6 month

Fig 5. Forest plots for (A) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (30% decrease), (B) WOMAC pain score (40% decrease), (C) International Knee Documentation Committee (IKDC) score at 6 months, (D) Knee Injury and Osteoarthritis Outcome Score (KOOS) at 6 months, and (E) visual analog scale (VAS) score at 6 months (CI, confidence interval; IV, inverse variance; M-H, Mantel-Haenszel.)

treated with PRGF.³⁵ In 1 of the prospective studies, it was observed that after 6 months of treatment, the visual analog scale score was significantly lower in the group treated with PRGF than in patients treated with HA.³⁷

The analysis of the remaining variables (Western Ontario and McMaster Universities Osteoarthritis Index scale for pain, function, and stiffness; Lequesne scale; Knee Injury and Osteoarthritis Outcome Score scale; and number of OMERACT-OARSI responders) showed a statistically significant superiority in the studies published in 2013 by Vaquerizo et al.³⁸ and Say et al.³⁷

Adverse Events

Although all studies included a safety analysis of the treatments administered, only 3 of these listed the adverse events.^{34,36,38} Overall, no severe adverse events were observed during the treatment and follow-up periods. The adverse events reported, both related and unrelated to treatment, were as follows: nonspecific low-back pain, febrile syndrome, other knee surgery, abdominal pain and dizziness, toothache, flu, knee and

hip pain, ankle sprain, renal colic, bronchitis, neck pain, itching of both outer thighs, headache, dizziness, urine infection, sciatica, cold, and pain after third injection. One study reported adverse events in 50 patients (26 in the group treated with PRGF and 24 in the control group).³⁶ No significant differences between treatments were found. In another study 16 adverse events were reported: 7 in the PRGF group and 9 in the control group.³⁸ The adverse events were generally mild and evenly distributed between the groups. Seven of 9 adverse events in the control group and all adverse events in the PRGF group were associated with the infiltration and were related to pain. Only 1 patient in the HA group withdrew from the study. Interestingly, in the study by Filardo et al.,³⁴ both procedures showed a statistically significant difference in the number of adverse events observed after the injections: both pain and swelling reaction were more frequent in the leukocyte-enriched PRP group than in the PRGF-treated group ($P = .0005$ for pain and $P = .03$ for swelling). Finally, the remaining 2 studies only included brief comments about adverse events that

seemed to be related to the injection procedure, such as pain and swelling of short duration.^{35,37} In any case, such events were resolved with the application of ice and acetaminophen (paracetamol).

Discussion

Summary of Evidence

This systematic review comprises 5 studies comparing the efficacy and safety of intra-articular injections of PRGF in the treatment of symptomatic knee OA against a control group. The findings suggest that PRGF is more effective than the treatments administered in the control group (HA or leukocyte-enriched PRP) regarding pain reduction. Although only 2 randomized clinical trials with Level I evidence are included in the systematic review,^{36,38} the results of these studies show a clear advantage of treatment with PRGF versus HA regarding the pain variable (Fig 3). Despite the quality of some of the included studies,^{35,37} the results are consistent with those obtained in randomized clinical trials. The study by Filardo et al.³⁴ compared PRGF treatment versus leukocyte-enriched PRP obtained by double centrifugation, and although the differences favored PRGF treatment, they did not reach statistical significance.

Recently, several systematic reviews and meta-analyses examining the efficacy of PRPs in several pathologies of the musculoskeletal system, including both joint cartilage degeneration³⁹⁻⁴¹ and muscle-, ligament-, and tendon-related conditions,^{15,16,42-49} have been published. The conclusions are varied but overall support the use of the technology in the treatment of mild to moderate knee OA, despite the inclusion of diverse platelet products that can lead to different clinical outcomes. The aim of our systematic review was to evaluate the clinical efficacy of a single platelet product (PRGF), therefore eliminating PRP-associated formulation variability. In addition, in contrast to the aforementioned reviews, this systematic review includes an updated review of the literature (October 2013) and at least 2 studies with high-quality evidence supporting the effectiveness and superiority of intra-articular infiltrations of PRGF versus HA in the treatment of symptomatic knee OA.^{36,38}

A highlight of this systematic review is the lack of relevant adverse events in the 530 patients included. With regard to the reported effects, they were always minor and were probably related to the infiltration process, regardless of the infiltrated substance. However, the study that compared the efficacy of 2 types of PRP, that is, PRGF versus leukocyte-enriched PRP, noted significant differences.³⁴ It has been observed that the incidence of adverse events related to pain and swelling increases in the group of patients receiving PRP containing leukocytes. The inclusion of

supraphysiological concentrations of leukocytes in the intra-articular space can generate transient inflammation, which in some cases could be reflected clinically, increasing patient discomfort.⁵⁰ It is especially important to avoid the inclusion of leukocytes in the treatment of diseases of the musculoskeletal system, such as OA, because their inclusion might not yield the optimal anabolic environment for disease treatment.^{10,51,52}

The mechanisms underlying the effectiveness of PRGF in the treatment of OA are not completely defined, but in the past 10 years of research, we have more evidence of different mechanisms of action. For example, the action on the canonical NF- κ B pathway could be behind the anti-inflammatory effect,⁵³ and the presence of endocannabinoids and related compounds could exert an antinociceptive effect, inhibiting the sensation of pain of the osteoarthritic joint.⁵⁴ The rich cocktail of morphogens and stem cell chemoattractant agents found in PRGF could also be essential in understanding the final outcome of the autologous approach. Recently, the combination of PRP and HA for synergistically enhancing the treatment of OA has been explored,⁵⁵ although clinical trials are necessary to support this promising combination.

Limitations

This systematic review has several limitations. First, the quality of a systematic review is affected by the quality of the primary data from the included studies. The quality of the 5 selected studies was assessed through qualified tools, and despite the fact that only 2 studies showed high quality in all the variables,^{36,38} the results of the 5 studies followed the same pattern in showing the superiority of PRGF over control in the treatment of pain. Beyond the methodologic quality, another possible limitation is the heterogeneity of the studies in terms of primary outcomes or treatment times. The greatest differences among the 5 studies were found in the control groups. The PRGF administration schedule differed among studies, ranging from 3 doses at a weekly interval^{35,36,38} to 3 doses every 3 weeks³⁴ or a single dose of treatment.³⁷ Patients receiving HA comprised the control groups, except in the study by Filardo et al.,³⁴ in which the control group received infiltration of 3 doses of leukocyte-enriched PRP (1 per week). Both the administration schedule and HA type differed markedly among studies. That is, the infiltrated HA was of low,³⁷ high,^{35,36} or very high molecular weight,³⁸ and different treatment schedules were followed, with either 3 weekly infiltrations³⁵⁻³⁷ or a single infiltration.³⁸ All this unevenness, together with the variability in the primary outcomes, did not allow us to carry out a formal meta-analysis.

The small number of studies that met the eligibility criteria is another drawback. Therefore more randomized

clinical trials of high quality should be performed to verify the effectiveness of PRGF; moreover, efforts must be dedicated to improving the optimal parameters in terms of number of doses and interval between doses. Finally, the absence of studies that met the inclusion criteria and included a control group receiving a placebo, for example, infiltration with physiological saline solution,³¹ might downplay the differences between groups because the control group, receiving either HA^{56,57} or leukocyte-enriched PRP,^{29,58} had proven clinical efficacy.

Conclusions

The current clinical evidence suggests that PRGF intra-articular infiltrations in patients with knee OA reduce pain and therefore are clinically efficacious in OA treatment.

References

1. Felson DT. Developments in the clinical understanding of osteoarthritis. *Arthritis Res Ther* 2009;11:203.
2. Goldring MB, Marcu KB. Epigenomic and microRNA-mediated regulation in cartilage development, homeostasis, and osteoarthritis. *Trends Mol Med* 2012;18:109-118.
3. Sandell LJ. Etiology of osteoarthritis: Genetics and synovial joint development. *Nat Rev Rheumatol* 2012;8:77-89.
4. Pereira D, Peleteiro B, Araujo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: A systematic review. *Osteoarthritis Cartilage* 2011;19:1270-1285.
5. Wielage RC, Myers JA, Klein RW, Happich M. Cost-effectiveness analyses of osteoarthritis oral therapies: A systematic review. *Appl Health Econ Health Policy* 2013;11:593-618.
6. Hilgsmann M, Cooper C, Arden N, et al. Health economics in the field of osteoarthritis: An expert's consensus paper from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin Arthritis Rheum* 2013;43:303-313.
7. Filardo G, Kon E, Roffi A, Di Matteo B, Merli ML, Marcacci M. Platelet-rich plasma: Why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc* in press, available online 26 November, 2013. <http://dx.doi.org/10.1007/s00167-013-2743-1>.
8. Smyth NA, Murawski CD, Fortier LA, Cole BJ, Kennedy JG. Platelet-rich plasma in the pathologic processes of cartilage: Review of basic science evidence. *Arthroscopy* 2013;29:1399-1409.
9. Zhu Y, Yuan M, Meng HY, et al. Basic science and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: A review. *Osteoarthritis Cartilage* 2013;21:1627-1637.
10. Anitua E, Sánchez M, Orive G, Padilla S. A biological therapy to osteoarthritis treatment using platelet-rich plasma. *Expert Opin Biol Ther* 2013;13:1161-1172.
11. Anitua E, Prado R, Sánchez M, Orive G. Platelet-rich plasma: Preparation and formulation. *Oper Tech Orthop* 2012;22:25-32.
12. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leukocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol* 2009;27:158-167.
13. Mishra A, Harmon K, Woodall J, Vieira A. Sports medicine applications of platelet rich plasma. *Curr Pharm Biotechnol* 2012;13:1185-1195.
14. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: The PAW classification system. *Arthroscopy* 2012;28:998-1009.
15. Chahal J, Van Thiel GS, Mall N, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: A systematic review with quantitative synthesis. *Arthroscopy* 2012;28:1718-1727.
16. Sheth U, Simunovic N, Klein G, et al. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: A meta-analysis. *J Bone Joint Surg Am* 2012;94:298-307.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009;339:b2700.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009;6:e1000097.
19. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039-1049.
20. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
21. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
22. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.
23. Jang SJ, Kim JD, Cha SS. Platelet-rich plasma (PRP) injections as an effective treatment for early osteoarthritis. *Eur J Orthop Surg Traumatol* 2013;23:573-580.
24. Cerza F, Carni S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012;40:2822-2827.
25. Filardo G, Kon E, Di Martino A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: Study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord* 2012;13:229.
26. Darabos N, Haspl M, Moser C, Darabos A, Bartolek D, Groenemeyer D. Intraarticular application of autologous conditioned serum (ACS) reduces bone tunnel widening after ACL reconstructive surgery in a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc* 2011;19(suppl 1):S36-S46.
27. Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: Intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc* 2010;18:472-479.

28. Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: Preliminary results in a group of active patients. *Sports Health* 2012;4:162-172.
29. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. *Arthroscopy* 2011;27:1490-1501.
30. Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: A pilot study. *Am J Phys Med Rehabil* 2010;89:961-969.
31. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. *Am J Sports Med* 2013;41:356-364.
32. Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 2012;91:411-417.
33. Wang-Saegusa A, Cugat R, Ares O, Seijas R, Cusco X, Garcia-Balletbo M. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. *Arch Orthop Trauma Surg* 2011;131:311-317.
34. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: Single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc* 2012;20:2082-2091.
35. Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: A retrospective cohort study. *Clin Exp Rheumatol* 2008;26:910-913.
36. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070-1078.
37. Say F, Gurler D, Yener K, Bulbul M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech* 2013;80:278-283.
38. Vaquerizo V, Plasencia MA, Arribas I, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: A randomized controlled trial. *Arthroscopy* 2013;29:1635-1643.
39. Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: A systematic review with quantitative synthesis. *Arthroscopy* 2013;29:2037-2048.
40. Chang KV, Hung CY, Aliwarga F, Wang TG, Han DS, Chen WS. Comparative effectiveness of platelet-rich plasma injections for treating knee joint cartilage degenerative pathology: A systematic review and meta-analysis. *Arch Phys Med Rehabil* 2014;95:562-575.
41. Dold AP, Zywiell MG, Taylor DW, Dwyer T, Theodoropoulos J. Platelet-rich plasma in the management of articular cartilage pathology: A systematic review. *Clin J Sport Med* 2014;24:31-43.
42. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: A systematic review of randomised controlled trials. *Lancet* 2010;376:1751-1767.
43. de Vos RJ, van Veldhoven PL, Moen MH, Weir A, Tol JL, Maffulli N. Autologous growth factor injections in chronic tendinopathy: A systematic review. *Br Med Bull* 2010;95:63-77.
44. Taylor DW, Petrera M, Hendry M, Theodoropoulos JS. A systematic review of the use of platelet-rich plasma in sports medicine as a new treatment for tendon and ligament injuries. *Clin J Sport Med* 2011;21:344-352.
45. Vavken P, Sadoghi P, Murray MM. The effect of platelet concentrates on graft maturation and graft-bone interface healing in anterior cruciate ligament reconstruction in human patients: A systematic review of controlled trials. *Arthroscopy* 2011;27:1573-1583.
46. Ahmad Z, Brooks R, Kang SN, et al. The effect of platelet-rich plasma on clinical outcomes in lateral epicondylitis. *Arthroscopy* 2013;29:1851-1862.
47. de Vos RJ, Windt J, Weir A. Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: A systematic review. *Br J Sports Med* 2014;48:952-956.
48. Hamid MS, Yusof A, Mohamed Ali MR. Platelet-rich plasma (PRP) for acute muscle injury: A systematic review. *PLoS One* 2014;9:e90538.
49. Vannini F, Di Matteo B, Filardo G, Kon E, Marcacci M, Giannini S. Platelet-rich plasma for foot and ankle pathologies: A systematic review. *Foot Ankle Surg* 2014;20:2-9.
50. Anitua E, Sánchez M, Prado R, Orive G. The type of platelet-rich plasma may influence the safety of the approach. *Knee Surg Sports Traumatol Arthrosc* in press, available online 9 May, 2012. <http://dx.doi.org/10.1007/s00167-012-2043-1>.
51. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. *J Bone Joint Surg Am* 2012;94:e1431-e1438.
52. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med* 2011;39:2135-2140.
53. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* 2013;9:721-730.
54. Descalzi F, Ulivi V, Cancedda R, et al. Platelet-rich plasma exerts antinociceptive activity by a peripheral endocannabinoid-related mechanism. *Tissue Eng Part A* 2013;19:2120-2129.
55. Andia I, Abate M. Knee osteoarthritis: Hyaluronic acid, platelet-rich plasma or both in association? *Expert Opin Biol Ther* 2014;14:635-649.

56. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—Meta-analysis. *Osteoarthritis Cartilage* 2011;19:611-619.
57. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006: CD005321.
58. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2011;19:528-535.