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

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Purpose: The purpose of this study was to compare the efficacy and safety in a randomized, clinical trial of 3 injections of PRGF-Endoret (BTI Biotechnology Institute, Vitoria, Spain) versus one single intra-articular injection of Durolane hyaluronic acid (HA) (Q-MED AB, Uppsala, Sweden) as a treatment for reducing symptoms in patients with knee osteoarthritis (OA). **Methods:** Ninety-six patients with symptomatic knee OA were randomly assigned to receive PRGF-Endoret (3 injections on a weekly basis) or one infiltration with Durolane HA. The primary outcome measures were a 30% decrease and a 50% decrease in the summed score for the pain, physical function, and stiffness subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Lequesne scores from baseline to weeks 24 and 48. The percentage of OMERACT-OARSI (Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative) responders was also documented. As secondary outcomes, pain, stiffness, and physical function by use of the WOMAC and the Lequesne score were considered and overall safety of the injection themselves. **Results:** The mean age of the patients was 63.6 years. Treatment with PRGF-Endoret was significantly more efficient than treatment with Durolane HA in reducing knee pain and stiffness and improving physical function in patients with knee OA. The rate of response to PRGF-Endoret was significantly higher than the rate of response to HA for all the scores including pain, stiffness, and physical function on the WOMAC, Lequesne index, and OMERACT-OARSI responders at 24 and 48 weeks. Adverse events were mild and evenly distributed between the groups. **Conclusions:** Our findings show that PRGF-Endoret is safe and significantly superior to Durolane HA in primary and secondary efficacy analysis both at 24 and 48 weeks; provides a significant clinical improvement, reducing patients' pain and improving joint stiffness and physical function with respect to basal levels in patients with knee OA; and should be considered in the treatment of patients with knee OA. **Level of Evidence:** Level I, multicenter randomized controlled clinical trial.

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Osteoarthritis (OA) of the knee can have a devastating impact on a patient's quality of life and increase the cost to society due to loss of work, early retirement, and arthroplasty.[1,2] The incidence of the disease is influenced by typical demographic parameters of developed countries including aging population and the epidemic of obesity.[3,4] Despite the societal and health care burden, there are no medical treatments that alter the course of the disease. The current therapeutic approaches focus on preventing or at least delaying the structural and functional changes of OA.[5]

The development and progression of OA are now believed to involve inflammation even in the early stages of the disease. There is a clear relation between

the progression of tibiofemoral cartilage damage and the presence of an inflammatory synovium.[6] The progressive destruction of cartilage involves degradation of extracellular matrix constituents, which in turn are responsible for propagating OA by inducing more inflammation.[7] There is sound rationale for the use of anti-inflammatory agents and therapies that reduce the inflammatory process and possibly promote the repair and regeneration of the degenerated cartilage.

Several studies describe the use of biological therapies such as platelet-rich plasma (PRP) as effective and safe methods in the treatment of pain and joint dysfunction caused by knee OA. There is an increasing amount of evidence supporting the potential of plasma rich in growth factors (PRGF-Endoret; BTI Biotechnology Institute, Vitoria, Spain), an autologous PRP characterized by the absence of leukocytes and proinflammatory cytokines and the presence of a specific dose of platelets and growth factors.[8] The use of this autologous biological therapy is associated with the potential to enhance tissue repair and reduce tissue inflammation.[9,10] Interestingly, Filardo et al.[11] observed in 2012 that injections of PRGF-Endoret in patients with knee OA led to a statistically significant improvement in all the scores evaluated at every follow-up visit. Moreover, they also found that when leukocytes were included in the PRP preparation, significantly more adverse events (involving pain and swelling) were detected. More recently, a randomized clinical trial evaluated and compared the efficacy and safety of PRGF-Endoret versus hyaluronic acid (HA) for the treatment of knee pain from OA.[12] The authors found that the rate of response was 14.1% points higher with a more enduring beneficial effect when compared with HA.

Recently, a new type of HA treatment based on a natural technology called non-animal stabilized hyaluronic acid (NASHA [Durolane; Q-MED AB, Uppsala, Sweden]) has been proposed.[13] The latter has been suggested to be effective for knee OA with just a single injection in each individual knee.[14,15]

The purpose of this study is to evaluate the safety and efficacy of PRGF-Endoret in the management of knee OA compared with Durolane. We hypothesized that 3 injections of PRGF-Endoret would be more effective in reducing pain and improving function than 1 injection of Durolane from baseline to week 48.

Methods

The study was carried out in accordance with the international standards on clinical trials: Real Decreto (Royal Decree) 223/2004, Declaration of Helsinki in its latest revised version (Seoul, 2008), and Good Clinical Practice Regulations (International Conference for Harmonization). The study protocol was reviewed and approved by the reference ethics committee. All patients provided written informed consent before entry into the study.

Patient Selection

Ninety-six patients were included in the study. Patients were considered eligible if they were aged older than 50 years and had OA of the knee as diagnosed based on the American College of Rheumatology criteria,[16] with radiographic confirmation of the Kellgren-Lawrence classification grade 2 to 4 (on a scale of 1 to 4, with higher numbers indicating more severe signs of the disease) (Table 1).

The patients were recruited and the study period was from July 2011 through November 2011, and patients returned for follow-up at 24 and 48 weeks. A preliminary assessment of each patient was carried out by an orthopaedic surgeon at the first basal visit, 30 days before randomization, and the medical history was completed. Patients were only included in the study if they met all the inclusion/exclusion criteria shown in Table 2. Each patient also received a booklet containing detailed instructions and of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. This booklet had to be completed by the patient and carried along with him or her at each of the subsequent visits.

Interventions

All patients who met the inclusion criteria (96 of 110 patients because 14 were excluded) were scheduled for their first treatment visit and received either of the 2 active treatments under study depending on the randomization made previously: injection of the affected knee with PRGF-Endoret (3 injections every 2 weeks) or injection of the affected knee with HA (Durolane) (a single injection).

To prepare the PRGF-Endoret technology, at each treatment visit, 36 mL of peripheral blood was extracted from each patient by venipuncture directly into 4 extraction tubes containing 3.8% sodium citrate as anticoagulant. The extracted blood was centrifuged at 580*g* for 8 minutes at room temperature in a BTI Biotechnology Institute system centrifuge. Once the blood tubes were centrifuged, we proceeded to physically separate the plasma fractions.

Only the 2 mL of PRGF-Endoret remaining above the red series and the "buffy coat" was taken, avoiding

Table 1. Description According to Kellgren-Lawrence Classification

Kellgren-Lawrence Classification	Global	PRGF	HA	*P* Value
2	32 (33.3%)	14 (29.2%)	18 (37.5%)	.665
3	47 (49%)	26 (54.2%)	21 (43.8%)	
4	17 (17.7%)	8 (16.7%)	9 (18.8%)	

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age >50 yr	Intra-articular HA injection in last 6 mo
Clinical symptoms >6 mo	Severe mechanical deformity
OA severity with Kellgren-Lawrence grade 2 to 4	Allergic or sensitive to HA-based product
No NSAIDs or steroid treatment in last 3 mo	Treatment with dicoumarin not to be reversed temporarily
	Polyarticular or infectious disease
	Systemic autoimmune rheumatic disease
	Blood dyscrasia
	Immunosuppressive (or immunodepressive) disease
	Body mass index >40
	Cancer/malignant lesions
	Difficulties in comprehension and/or reading and writing
	Physical impediments to answer questionnaire

NSAIDs, nonsteroidal anti-inflammatory drugs.

picking up the leukocytes. Before infiltration, we put all these 2-mL fractions together in a single tube (total of 8 mL), gently inverting the tube in a sterile glass container in which they were activated before infiltration, by adding 400 μL of calcium chloride. The volume of PRGF-Endoret injected was 8 mL.

The control group received a single injection of HA (Durolane). The Durolane is a high−molecular weight molecule obtained by non-animal stabilized hyaluronic acid technology. It is synthesized by bio-fermentation using non-pathogenic bacteria, streptococcus, and is subsequently purified. Durolane is characterized by the length of time it remains present in the joint space in which the bridges that cross the molecule increase its density and, hence, increase its concentration (60 mg/3 mL) in the joint space.

Regardless of the patient group, the injection technique was the same. For knee infiltration, patients were placed in a supine position. The knee was in extension using a classical external suprapatellar approach after skin disinfection with alcoholic chlorhexidine, with a 22-gauge needle. After infiltration, patients were asked to move the knee with flexion and extension exercises for 5 minutes to encourage content redistribution.

Randomization and Allocation Concealment

During the patient visits, the treatment assigned by randomization was delivered. A simple randomization was carried out. Both the evaluators and patients remained blinded to the assignment of treatments. A patient number identified all patients included in the study after signing the informed consent form. Each patient was identified by a numerical code. The correspondence between the number of patients and their treatment was performed by use of specific software for randomization, keeping that relation in a sealed envelope. This envelope was not opened until the moment before the treatment was applied. The response was assessed by researchers not involved in the application of treatment (blinded). In the data report forms, there was no reference to the treatment that had been applied.

Outcome Measures

Efficacy Assessment. The primary efficacy outcomes were defined as the percentage of patients having a 30% decrease and a 50% decrease in the summed score for all the WOMAC subscales—pain, stiffness, and physical function—as well as the Lequesne score, from baseline to 24 and 48 weeks. This outcome was measured by applying the WOMAC questionnaire, which compared results with baseline therapy based on the criteria of the Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI).[17-19] The secondary efficacy outcomes included the scores on the WOMAC subscales for pain, stiffness, and physical function and the Lequesne index. We use these questionnaires because they are internationally validated to assess the treatment of knee OA. They have also been translated into Spanish.

Safety Assessments. The nature, onset, duration, severity, and outcomes of all adverse events, as well as any association of an adverse event related to the study medication, were assessed and documented at each visit. To evaluate the safety profile of the treatments, all complications and adverse events were recorded with an accountability scale. The use of rescue medication was recorded daily in the patients' diaries.

Power Analysis

To calculate the number of patients, the parameters obtained in the study of Wang-Saegusa et al.[20] were taken as reference. We estimated a sample size of 48 patients per group to provide at least 80% power to detect differences in the WOMAC pain scale superior to 1.2 for PRGF-Endoret infiltration versus HA, at a 5% level of significance, taking into consideration 10% possible losses.

Data Analysis

Initially, a descriptive analysis of the sample was performed taking into account the demographic and clinical variables of the patients. Quantitative variables (age, body mass index) were determined by the mean, standard deviation, and range, and for qualitative variables (gender, labor activity, history, medication type, and severity of radiologic OA), a frequencies analysis was conducted.

Analysis of the primary outcome measure was conducted according to the protocol. The baseline comparability of treatment groups was performed by applying a Student *t* test for quantitative variables and a χ^2 analysis for categorical variables. The primary efficacy variable was assessed with a χ^2 test. Secondary efficacy variables were evaluated with either a χ^2 test for qualitative variables or a Student *t* test for quantitative variables. For all outcomes, a nominal *P* value of less than .05 was considered to indicate statistical significance.

Results

Patient Characteristics

A total of 110 patients were initially screened, and 14 were excluded; thus 96 patients underwent randomization and treatment and completed the follow-up. The most common reason for exclusion (8 patients) was incomplete follow-up (Fig 1). The mean age was 63.6 years (range, 50 to 84 years), the mean body mass index was 30.9 (range, 20.7 to 42.9), and in both groups the percentage of women was higher (66.7% and 54.2% for PRGF-Endoret and HA groups, respectively). As shown in Table 3, the groups were balanced in terms of age, gender, body mass index, previous infiltrations, Kellgren-Lawrence grade, and WOMAC and Lequesne scores. Only 1 patient was withdrawn from the HA group.

Clinical Outcomes at 24 Weeks

Results of primary and secondary outcome measures at 24 weeks for the entire study population and all WOMAC and Lequesne scores are summarized in Table 4. Regarding the primary outcome measures (including the percentage of patients having 30% and 50% decreases in the summed score for the WOMAC pain, physical function, and stiffness subscales and Lequesne scores from baseline to week 24), the results were significantly different for both treatment groups. In the case of patients having a 30% decrease, the rate of response to PRGF-Endoret was 66 percentage points (95% confidence interval [CI], 48 to 84; $P < .001$), 43 percentage points (95% CI, 23 to 64; $P < .001$), and 23 percentage points (95% CI, 2 to 47; $P = .02$) higher than the rate of response to HA for the WOMAC pain, physical function, and stiffness subscales, respectively. In the case of patients having a 50% decrease, the rate of response to PRGF-Endoret was 43 percentage points (95% CI, 25 to 62; $P < .001$), 29 percentage points

Table 3. Baseline Characteristics of Patients

Characteristic	PRGF-Endoret	HA	*P* Value
Age (yr)	62.4 ± 6.6	64.8 ± 7.7	.112
Gender (% female)	32 (66.7%)	26 (54.2%)	.215
Body mass index (kg/m^2)	30.7 ± 3.6	31.0 ± 4.6	.727
Primary arthritis	21 (44%)	20 (42%)	.839
Kellgren-Lawrence grade	2.6 ± 7.1	2.8 ± 0.7	.665
WOMAC score			
Pain subscale	9.6 ± 2.5	10.2 ± 3.5	.373
Stiffness subscale	3.7 ± 1.7	4.0 ± 2.0	.102
Physical function subscale	32.6 ± 9.9	36.7 ± 13.7	.382
Global	45.9 ± 12.7	50.8 ± 18.4	.137
Lequesne index*	12.8 ± 3.8	13.1 ± 38	.738
No. of patients	48	48	

NOTE. Quantitative variables are expressed as mean ± standard deviation. Qualitative variables are shown as absolute and relative frequencies. $P < .05$ is considered statistically significant.

*The Lequesne score is an index of severity for knee OA that includes 3 subscales (pain or discomfort, maximum distance walked, and activities of daily living). To assess the severity of gonarthrosis, we determined the sum of all points, with a minimum score of 0 points and a maximum score of 24 points (0 points, no severity; 1 to 4 points, mild; 5 to 7 points, moderate; 8 to 10 points, severe; 11 to 13 points, very severe; and 14 points or greater, extremely severe).

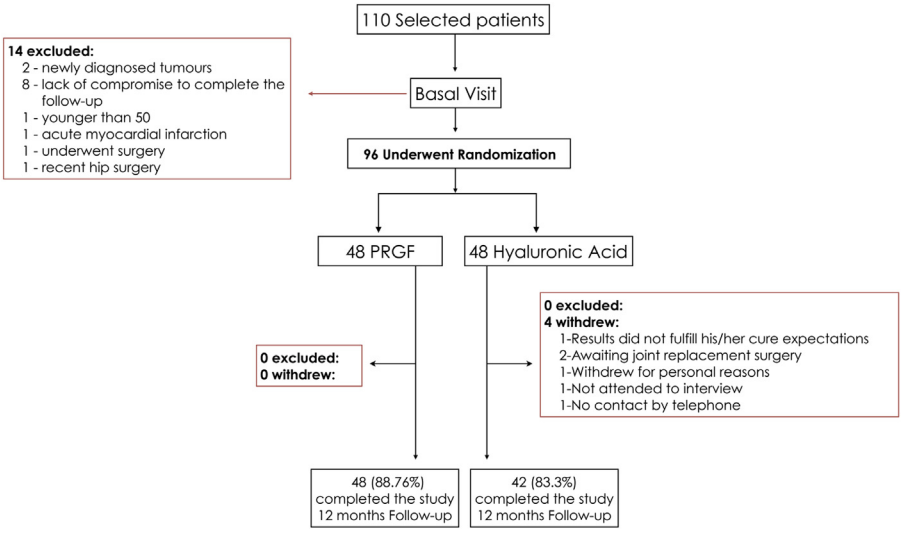

Fig 1. Enrollment and outcomes.

Table 4. Primary and Secondary Outcomes at 24 Weeks

	PRGF-Endoret	HA	IC (95% CI)	*P* Value
No. of patients (all randomized patients)	48	48		
Primary outcome [No. (%)]				
30% decrease in WOMAC pain score	40 (83)	7 (17)	66 (48-84)	< .001
30% decrease in WOMAC physical function score	29 (60)	7 (17)	43 (23-64)	< .001
30% decrease in WOMAC stiffness score	24 (52)	11 (27)	23 (2-47)	.020
30% decrease in Lequesne index	35 (73)	7 (17)	56 (36-75)	< .001
50% decrease in WOMAC pain score	26 (54)	5 (11)	43 (25-62)	< .001
50% decrease in WOMAC physical function score	19 (40)	5 (11)	29 (11-48)	.001
50% decrease in WOMAC stiffness score	16 (35)	7 (16)	19 (0-37)	.035
50% decrease in Lequesne index	14 (29)	2 (4)	25 (9-41)	.002
OMERACT-OARSI responders*	40 (83)	13 (27)	56 (38-75)	< .001
Secondary outcome				
WOMAC pain score				
% Change from baseline	48.8 ± 26.3	−1.6 ± 42.7	50.4 (35.7-65.0)	< .001
End of follow-up	5.0 ± 3.1	10.3 ± 4.8	−5.2 (−6.9-3.5)	< .001
WOMAC stiffness score				
% Change from baseline	25.7 ± 46.3	−6.3 ± 61.2	32.0 (9.4-54.5)	.006
End of follow-up	2.5 ± 1.7	4.0 ± 2.3	−1.5 (−2.3-0.7)	< .001
WOMAC physical function score				
% Change from baseline	40.5 ± 29.3	−1.4 ± 41.6	41.9 (27.2-56.6)	< .001
End of follow-up	19.7 ± 11.1	36.2 ± 16.8	−16.5 (−22.4-10.6)	< .001
WOMAC total score				
% Change from baseline	42.0 ± 26.9	−0.8 ± 39.1	42.9 (29.2-56.5)	< .001
End of follow-up	27.2 ± 15.1	50.4 ± 23.2	−23.2 (−31.3-15.1)	< .001
Lequesne index†				
% Change from baseline	38.6 ± 20.4	−3.1 ± 33.4	41.6 (30.2-53.1)	< .001
End of follow-up	5.2 ± 3.4	5.4 ± 3.3	−5.5 (−7.3-3.7)	< .001

NOTE. A primary response was defined as the percentage of patients having a 30% decrease and a 50% decrease in the summed score for the WOMAC pain, physical function, and stiffness subscales and Lequesne scores from baseline to week 24. Quantitative variables are expressed as mean ± standard deviation. Qualitative variables are shown as absolute and relative frequencies. $P < .05$ is considered statistically significant.

IC, confidence interval.

*Outcome Measures in Rheumatology Clinical Trials—Osteoarthritis Research Society and Health Assessment Questionnaire.

†The Lequesne score is an index of severity for knee OA that includes 3 subscales (pain or discomfort, maximum distance walked, and activities of daily living). To assess the severity of gonarthrosis, we determined the sum of all points, with a minimum score of 0 points and a maximum score of 24 points (0 points, no severity; 1 to 4 points, mild; 5 to 7 points, moderate; 8 to 10 points, severe; 11 to 13 points, very severe; and 14 points or greater, extremely severe).

(95% CI, 11 to 48; $P = .001$), and 19 percentage points (95% CI, 0 to 37; $P = .035$) higher than the rate of response to HA for the WOMAC pain, physical function, and stiffness subscales, respectively. Significant differences were also observed in the Lequesne score. In the case of patients with a 30% decrease, the rate of response was 56 percentage points (95% CI, 36 to 75; $P < .001$) higher for the PRGF-Endoret group, whereas in the evaluation of patients with a 50% decrease, the rate of response was 25 percentage points (95% CI, 9 to 41; $P = .002$) higher for the PRGF-Endoret group. Furthermore, the percentage of OMERACT-OARSI responders was 83.3% in the PRGF-Endoret group and 27.08% in the HA group (difference, 56 percentage points; 95% CI, 38 to 75; $P < .001$).

Regarding the secondary outcome measures, the rate of response to PRGF-Endoret was significantly higher than the rate of response to Durolane HA for all the scores. In particular, the WOMAC pain score was reduced to half in the PRGF-Endoret group (from 9.6 ± 2.5 to 5.0 ± 3.1), whereas it was invariable in the HA group (from 10.3 ± 4.8 to 10.2 ± 3.5).

Clinical Outcomes at 48 Weeks

The results obtained at 48 weeks followed the same trend as those reported at 24 weeks (Table 5). In fact, the results from all primary outcome measures were significantly different for both treatment groups. In the case of patients having a 30% decrease, the rate of response to PRGF-Endoret was 46 percentage points (95% CI, 27 to 66; $P < .001$), 37 percentage points (95% CI, 17 to 58; $P < .001$), and 40 percentage points (95% CI, 20 to 60; $P < .001$) higher than the rate of response to HA for the WOMAC pain, physical function, and stiffness subscales, respectively. In the case of patients having a 50% decrease, the rate of response to PRGF-Endoret was 29 percentage points (95% CI, 13 to 45; $P < .001$), 31 percentage points (95% CI, 16 to 47; $P < .001$), and 28 percentage points (95% CI, 11 to 46; $P = .001$) higher than the rate of response to HA for

Table 5. Primary and Secondary Outcomes at 48 Weeks

	PRGF-Endoret	HA	IC (95% CI)	*P* Value
No. of patients (randomized patients available for follow-up)	48	42		
Primary outcome: total OARSI responders [No. (%)]				
30% decrease in WOMAC pain score	28 (58.3)	5 (11.9)	46 (27-66)	< .001
30% decrease in WOMAC physical function score	26 (54.2)	7 (16.7)	37 (17-58)	< .001
30% decrease in WOMAC stiffness score	24 (52.2)	5 (12.2)	40 (20-60)	< .001
30% decrease in Lequesne index	23 (47.9)	1 (2.4)	46 (28-63)	< .001
50% decrease in WOMAC pain score	15 (31)	1 (2)	29 (13-45)	< .001
50% decrease in WOMAC physical function score	15 (31)	0 (0)	31 (16-47)	< .001
50% decrease in WOMAC stiffness score	16 (33)	2 (5)	28 (11-46)	.001
50% decrease in Lequesne index	9 (19)	1 (2)	17 (2-31)	.017
OMERACT-OARSI responders*	33 (69)	9 (21)	48 (27-68)	< .001
Secondary outcome				
WOMAC pain score				
% Change from baseline	33.5 ± 30.9	−11.1 ± 41.2	48.98 (32.37-65.59)	< .001
End of follow-up	6.3 ± 3.3	10.7 ± 3.7	−4.8 (−6.38- −3.23)	< .001
WOMAC stiffness score				
% Change from baseline	24.6 ± 40.4	−34.1 ± 64.7	69.8 (42.2-97.5)	< .001
End of follow-up	2.6 ± 1.4	4.7 ± 2.0	−2.31 (−3.11- −1.51)	< .001
WOMAC physical function score				
% Change from baseline	33.7 ± 28.7	−13.0 ± 40.8	51.47 (36.64-66.31)	< .001
End of follow-up	21.9 ± 11.3	38.9 ± 14.2	−18.88 (−24.61-13.15)	< .001
WOMAC total score				
% Change from baseline	34.0 ± 27.6	−12.9 ± 36.7	51.24 (37.25-65.23)	< .001
End of follow-up	30.8 ± 15.5	54.2 ± 19.2	−26.00 (−33.76-18.24)	< .001
Lequesne index†				
% Change from baseline	30.1 ± 23.0	−15.6 ± 31.2	−48.36 (34.80-61.91)	< .001
End of follow-up	8.9 ± 3.7	14.4 ± 3.8	−6.05 (−7.76- −4.34)	< .001

NOTE. A primary response was defined as the percentage of patients having a 30% decrease and a 50% decrease in the summed score for the WOMAC pain, physical function, and stiffness subscales and LEQUESNE scores from baseline to week 48. Quantitative variables are expressed as mean ± standard deviation. Qualitative variables are shown as absolute and relative frequencies. $P < .05$ is considered statistically significant.

IC, confidence interval.

*Outcome Measures in Rheumatology Clinical Trials—Osteoarthritis Research Society and Health Assessment Questionnaire.

†The Lequesne score is an index of severity for knee OA that includes 3 subscales (pain or discomfort, maximum distance walked, and activities of daily living). To assess the severity of gonarthrosis, we determined the sum of all points, with a minimum score of 0 points and a maximum score of 24 points (0 points, no severity; 1 to 4 points, mild; 5 to 7 points, moderate; 8 to 10 points, severe; 11 to 13 points, very severe; and 14 points or greater, extremely severe).

the WOMAC pain, physical function, and stiffness subscales, respectively. Differences were also significant for the Lequesne index. In the case of patients with a 30% decrease, the rate of response was 46 percentage points (95% CI, 28 to 63; $P < .001$) higher for the PRGF-Endoret group, whereas in the evaluation of patients with a 50% decrease, the rate of response was 19 percentage points in the PRGF-Endoret group versus 2 percentage points in the HA group. Interestingly, the percentage of OMERACT-OARSI responders was 69% in the PRGF-Endoret group and 21% in the HA group (difference, 48 percentage points; 95% CI, 27 to 68; $P < .001$).

Regarding the secondary outcome measures, significant differences were observed for WOMAC pain scores between both treatment groups. Indeed, the WOMAC pain score was reduced from the basal level, from 9.6 ± 2.5 to 6.3 ± 3.3 (35% decrease), whereas it was increased in the HA group (from a basal level of 10.3 ± 4.8 to 10.7 ± 3.7). In addition, the rate of response to PRGF-Endoret was significantly higher ($P < .001$) than the rate of response to Durolane HA for the remaining scores.

Figure 2 summarizes the evolution of the main efficacy variables from baseline to weeks 24 and 48.

Adverse Effects

Sixteen adverse events, 7 in the PRGF-Endoret group and 9 in the HA group, were reported during the study, as shown in Table 6. Adverse events were generally mild and evenly distributed between the groups ($P = .610$). Seven of 9 adverse events in the HA group and all the events in the PRGF-Endoret group were related to pain associated with the infiltration. Only 1 patient from the HA group withdrew from the study.

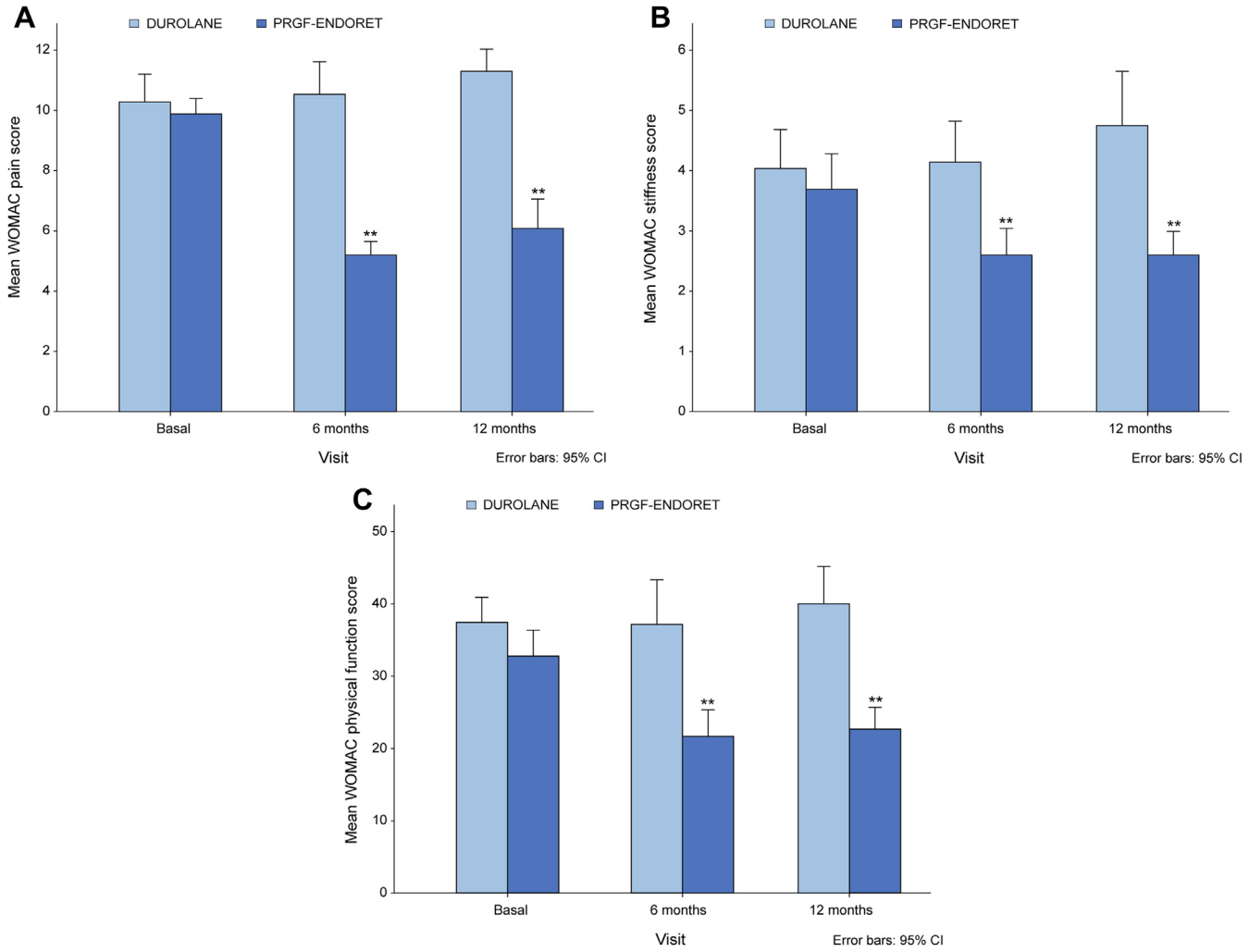

Fig 2. Evolution of efficacy outcomes. (A) Mean WOMAC pain, (B) mean WOMAC stiffness, and (C) mean WOMAC physical function scores.

Discussion

The results from this randomized trial show that the treatment based on 3 intra-articular injections of the autologous biological therapy, plasma rich in growth factors (PRGF-Endoret), is significantly more efficient than 1 single injection of Durolane HA in reducing knee pain and stiffness and improving physical function in patients with knee OA. In fact, the rate of response to PRGF-Endoret was significantly higher than the rate of response to HA for all the scores including the WOMAC pain, physical function, stiffness subscales; WOMAC total; and Lequesne index, as well as the percentage of OMERACT-OARSI responders. Furthermore, we observed that injection of arthritic knees with PRGF-Endoret shows a longer beneficial effect than HA because the results obtained at 48 weeks were also significantly different for all the scores.

Although clinically meaningful pain relief is in general defined as a reduction in pain intensity of more than 30% from the baseline level,[21,22] a reduction of 50% is considered a significant improvement in pain according to the OMERACT-OARSI criteria, with a direct translation to the overall improvement of the patient's quality of life. Therefore we decided to analyze both subsets of patients with 30% and 50% improvements in the principal WOMAC subscores (pain, physical function, and stiffness). All the secondary variables were also significantly improved after PRGF-Endoret treatment: the rates of OMERACT-OARSI responders were 56 and 48 percentage points higher in the PRGF-Endoret group than in the HA group at 24 and 48 weeks, respectively. On the other hand, the majority of adverse events that were reported by patients were mild in severity and not related to the type of treatment.

In the past few years, the use of PRP products and especially PRGF-Endoret technology has been extended to the treatment of different musculoskeletal injuries.[20,23-25] An increasing number of studies suggest that apart from the mechanical stress, many of the autologous growth factors and proteins released from the

Table 6. Adverse Events

Group	Adverse Event	Grade	Relation to Infiltration	Evolution
Durolane				
Patient 3	Postinjective pain reaction	Moderate	Yes	Resolved
Patient 19	Postinjective pain reaction	Mild	Yes	Resolved
Patient 31	Pseudoseptic reactions	Moderate	Yes	Resolved
Patient 39	Postinjective pain reaction	Mild	Yes	Resolved
Patient 67	Postinjective pain reaction	Mild	Yes	Resolved
Patient 72	Pseudoseptic reactions	Moderate	Yes	Resolved
Patient 83	Postinjective pain reaction	Mild	Yes	Resolved
Patient 95	Postinjective pain reaction	Mild	Yes	Resolved
PRGF-Endoret				
Patient 13	Postinjective pain reaction	Mild	Yes	Resolved
Patient 24	Postinjective pain reaction	Mild	Yes	Resolved
Patient 36	Postinjective pain reaction	Mild	Yes	Resolved
Patient 50	Postinjective pain reaction	Moderate	Yes	Resolved
Patient 53	Postinjective pain reaction	Mild	Yes	Resolved
Patient 57	Postinjective pain reaction	Mild	Yes	Resolved
Patient 68	Postinjective pain reaction	Mild	Yes	Resolved
Patient 75	Postinjective pain reaction	Mild	Yes	Resolved

fibrin scaffold of PRGF-Endoret may play a pivotal role in the repair or regeneration of the damaged cartilage. For example, platelet-derived growth factor promotes chondrocyte proliferation and the maintenance of their hyaline-like phenotype.[26] Insulin-like growth factor (IGF-I) stimulates proteoglycan synthesis,[27] whereas transforming growth factor (TGF-β) exerts a critical role on mesenchymal stem cell differentiation and matrix deposition.[28] Despite this, the pool of biologically active molecules from PRGF-Endoret may decrease nuclear factor κB activation, a major pathway involved in the pathogenesis of OA, which is characterized by a catabolic and inflammatory joint environment.[29] Last but not least, the supernatant of autologous proteins also reduces the suppressive effects of interleukin 1 on proteoglycan synthesis in cartilage.[30]

This randomized clinical trial reinforces the idea that PRGF-Endoret is effective in the treatment of patients with OA of the knee, with the beneficial effects persisting for 48 weeks. This autologous technology has European Community and Food and Drug Administration clearance to be used for the treatment of musculoskeletal injuries and more particularly for the treatment of OA.

Limitations

The limitations of this study include the lack of a placebo group; the use of Durolane as HA, which makes comparisons with other studies difficult; and the lack of measurement of physical activity levels in patients after applying the treatments. Moreover, the final study population was smaller than the population we had previously estimated. However, this study included patients who had the highest degree of severity on radiography (Alback grade 4) and evaluated both treatments during a 48-week period, highlighting their long-term efficacy and safety outcomes. It is true that the different dosages used in both treatment groups (one receiving one single injection *v* the other receiving 3 consecutive injections) makes it impossible to blind the patients, but the evaluation of the patients' status and disease progression was performed by physicians in a blinded way.

Conclusions

Our findings show that PRGF-Endoret is safe and significantly superior to Durolane HA in primary and secondary efficacy analysis both at 24 and 48 weeks, and it provides a significant clinical improvement, reducing patients' pain and improving joint stiffness and physical function, with respect to basal levels in patients with knee OA. In addition, the efficacy of PRGF-Endoret has been shown in patients with Kellgren-Lawrence classification grade 2 to 4. Therefore we suggest that this biological treatment should be considered in the treatment of patients with knee OA.

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