Pain Ther (2025) 14:675–690
https://doi.org/10.1007/s40122-024-00699-y

ORIGINAL RESEARCH

# A Long-Term Retrospective Observational Clinical Study Evaluating the Efficacy of Plasma Rich in Growth Factors (PRGF) in the Treatment of Back Pain

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Received: October 22, 2024 / Accepted: December 11, 2024 / Published online: January 16, 2025


## ABSTRACT

***Introduction***: Chronic back pain is a long-lasting disorder that is significantly associated with a reduction in the quality of life. Previously, the efficacy of intradiscal and epidural injections of plasma rich in growth factors (PRGF) was demonstrated at 6 months. The objective of this study was to retrospectively examine the medical records of these patients in order to determine whether the observed improvement at the 6-month follow-up was sustained over time.

***Methods***: PRGF efficacy was evaluated using validated questionnaires: Core Outcome Measure Index (COMI) Pain score, COMI Disability score, COMI total score, and Oswestry Disability Index (ODI). Furthermore, an evaluation was conducted to determine whether the patients had undergone additional treatments.

***Results***: the results demonstrated that 85.2% of the 27 patients who were enrolled exhibited sustained improvement across all scales over a median follow-up period of 24 months. The results of all questionnaires administered at 24 months exhibited statistically significant differences when compared to the baseline data ($p<0.01$). Furthermore, there were no statistically significant differences

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40122-024-00699-y.

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between the results reported at 6 months and those at 24 months ($p>0.05$).
***Conclusions***: the results of this retrospective study demonstrate that treatment of chronic back pain with PRGF was effective in maintaining pain reduction and improving function for at least 24 months after the end of treatment.

**Keywords:** Back pain; Degenerative disc disease; Growth factors; Intervertebral disc degeneration; Platelet-rich plasma; PRGF; PRP; Regenerative medicine

**Key Summary Points**

*Why carry out this study?*

Chronic back pain is a very prevalent disease that presents a significant social and economic burden and is continually growing due to lifestyle habits and the progressive aging of the population.

Regenerative medicine offers biological therapies utilizing blood derivatives, such as plasma rich in growth factors (PRGF) as a solution for treating chronic back pain. These therapies are minimally invasive and autologous, representing an innovative biological approach to pain management.

The purpose of the present study was to retrospectively examine patient records and determine whether the improvement observed in the patients treated with PRGF was sustained over time.

*What was learned from the study?*

Previous studies have shown that intradiscal and epidural infiltration of PRGF significantly reduces chronic back pain and physical disability for at least 6 months.

The present study supports the findings of the previous prospective study and provides additional data on long-term effects, as the improvement in all scales evaluated was maintained in the majority of patients (85.2%) over a mean follow-up period of 24 months.

## INTRODUCTION

The social and economic burden of chronic back pain is considerable and continues to grow, primarily due to lifestyle habits and the progressive aging of the population. This condition is identified as one of the ten leading causes of disability-adjusted life years (DALYs) worldwide, ranking fourth after ischemic heart disease, cerebrovascular disease, and lower respiratory tract infections [1]. The prevalence of back pain throughout a person's life is variable, ranging from 11 to 84% [2]. It is associated with increased healthcare costs and is a leading cause of sick leave in both high- and low-income countries. In the United States in 2016, pathology generated the most healthcare spending among 154 diseases, at a cost of approximately $134.5 billion [3]. This figure does not include indirect costs such as sick leave and lost productivity [4]. For all these reasons, there is a great deal of motivation—medical, social, and economic—to find effective treatments for the reduction of chronic low back pain.

The current management of chronic back pain comprises a range of non-pharmacological interventions, including physiotherapy, activity modification, and electrotherapy, in addition to pharmacological treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, opioids, and corticosteroids [5–7]. In cases where conservative treatments have been unsuccessful, interventional procedures may be considered, including epidural steroid injections, nerve blocks, or radiofrequency ablation [5, 6]. All these treatments have certain limitations and variable results. The emergence of promising new biologically inspired, minimally invasive strategies offers an opportunity to

overcome the current limitations of conventional treatments and address unmet medical needs. These strategies aim to tackle the underlying causes of the lesions, with the potential to reduce both recovery time and the number of recurrences. The incorporation of regenerative medicine strategies, particularly platelet-rich plasma (PRP), has demonstrated efficacy in the treatment of chronic back pain [8–12]. The use of PRP involves the administration of growth factors and other anti-inflammatory biomolecules with the aim of not only alleviating pain but also restoring functionality [13, 14].

A groundbreaking biological approach in this field is plasma rich growth factors (PRGF) technology, which has been applied in several areas of medicine for more than 25 years [15], including pathologies of the musculoskeletal system [16–18], such as cervical and low back pain [19–22]. PRGF technology represents a paradigm of orthobiologics [23] since it is a type of PRP in which platelets are moderately concentrated and both erythrocytes and leukocytes are removed. Finally, activation with calcium chloride allows both the activation of the coagulation cascade and the controlled release of platelet growth factors [24].

Recently, our research group has conducted a prospective observational study with a 6-month follow-up period to demonstrate the efficacy of intradiscal and epidural PRGF infiltrations in patients with chronic clinical symptoms due to intervertebral disc (IVD) degeneration [22]. In this study, 87.5% of patients exhibited a reduction in pain on the Numeric Rating Scale (NRS) scale exceeding 30%, which is considered to be the minimal clinically important change (MCIC), starting from a median of 8 and ending at 6 months with a value of 2 points [22]. These encouraging results observed during the follow-up period with respect to pain, functionality and quality of life have prompted us to explore the long-term evolution of these patients, assuming that there is substantial evidence indicating that chronic back pain is a condition that typically persists throughout an individual's lifetime, with a high probability of recurrence [25, 26]. Accordingly, the objective of the present study was to retrospectively examine the medical records of patients who had participated in our previous 6-month prospective study to ascertain whether the observed improvement at the 6-month follow-up was sustained over time. For this purpose, we surveyed the same questionnaires and evaluated whether the patients had experienced recurrences and/or received additional treatments.

## METHODS

### Study Design and Patient Population

This study was a retrospective observational study of a previously prospective study [22] carried out in a single private center in Vitoria (Spain). The protocol of this retrospective study (code BTIIMD-01-ER-24-DISC2) was approved in July 2024, by the Institutional Review Board (CEIm-E) and conducted in accordance with the revised World Medical Association Declaration of Helsinki, amended in 2013 in Brazil [27]. To obtain the data for this study, patients provided informed consent for the review of their medical records. This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (Supplementary Table S1) [28]. The inclusion criteria for the participation in this retrospective study were as follows: (a) patients who have previously participated in the "*Prospective observational follow-up study to evaluate the effectiveness and effects on quality of life of intradiscal infiltrations of PRGF-Endoret in the treatment of disc degeneration*" with code BTIIMD_02_EP/20/DISC [22], (b) patients who have completed the follow-up (6 months) of such study, (c) patients who have signed the informed consent for the present study, and (d) patients who have filled out at least one evaluation scale after the completion of the follow-up of that prospective study. The exclusion criterion was the absence of data on the variables to be studied.

The inclusion and exclusion criteria for participation in the prospective study have been previously reported [22]. Inclusion criteria: (a) patients over 18 years of age, (b) patients diagnosed with intervertebral disc degeneration by magnetic resonance imaging (MRI), (c) patients

with positive visible MRI signs, including rupture of the annulus fibrosus, annular fissure, with or without disc herniation in its protrusive form, (d) symptoms of 3 months of evolution that has not responded to conventional pharmacological treatment, (e) numerical pain scale (NRS) between 6 and 10, average of the last month, (f) a complete blood test carried out in the last 2 months, (g) informed consent form signature, and (h) agreement in the informed consent to be available for post-treatment follow-up for 6 months. Exclusion criteria: (a) presence of lumbar fracture, extruded disc herniations and herniations with signs of calcification, (b) patients who have previously undergone spinal surgery or lumbar rhizolysis within the last 8 months, (c) patients with severe cardiovascular diseases, central nervous system diseases, epilepsy, coagulopathies, immunological diseases, infectious diseases (e.g., hepatitis, HIV, syphilis) and cancer, (d) patients with a history of drug use (e.g., alcoholism or other) and mental illness or marked psychological conditions related to pain, (e) morbidly obese patients, (f) women who are pregnant or breastfeeding or women of childbearing age who are not taking contraceptive measures, and (g) pathologies that produce marked alterations in the efficacy of PRGF or coagulation, such as poorly controlled diabetes mellitus (glycosylated hemoglobin greater than 9%), hematological alterations (thrombopathy, thrombopenia, anemia with Hb < 9), being subjected to immunosuppressive and/or di-coumarinic treatments, or any treatment with corticoids during the 6 months prior to inclusion in the study.

### Preparation and Characterization of PRGF

The details about the preparation and characterization of PRGF were previously reported [22]. In brief, peripheral venous blood was collected in eight 9-ml tubes containing 400 µl of sodium citrate (3.8% w/vol) as an anticoagulant (EDK2_ENV kit, BTI Biotechnology Institute, S.L., Vitoria, Spain) and centrifuged for 8 min at 580 g (Endoret System V). Next, the upper plasma volume was discarded (Fraction F1), and the 2 ml plasma fraction located just above the buffy coat (Fraction F2) was collected without the inclusion of leukocytes or erythrocytes. Finally, PRGF was activated just prior to infiltration through the addition of 20 µl calcium chloride (10% w/vol) per milliliter of PRGF. PRGF was characterized by hematological analysis (complete blood count with five-part differential) (Pentra ES 60, Horiba ABX SAS, Montpelier, France) of both peripheral blood and non-activated liquid PRGF (F1 and F2) [22].

### PRGF Infiltration Technique

The complete infiltration protocol was described by Anitua et al. in 2023 [22]. First, the patients were sedated, and antibiotic prophylaxis was administered. Briefly, PRGF infiltrations were conducted under fluoroscopic guidance with the patient positioned prone for the lumbar region and supine for the cervical area. Once placed the tip of the spinal needle in the depth of the nucleus pulposus, 3 ml of freshly activated PRGF (fraction F2) were injected into each degenerated disc without the use of any type of contrast agent. This procedure was performed on up to three levels. Following this, fluoroscopic lateral imaging was used to guide the epidural infiltration of 2 ml of freshly activated PRGF (fraction F2). After treatment, the patient was kept in the recovery room for 1–2 h. Later, analgesics were prescribed depending on the clinical evolution. Each patient received a series of 2–3 biweekly infiltrations depending on the patient's clinical status [22].

### Follow-Up and Outcome Measures

The efficacy of the treatment was evaluated using validated patient-reported outcomes (PRO): the Spine Tango Core Outcome Measure Index (COMI) questionnaire, the Numeric Rating Scale (NRS) for back pain (COMI Pain score), and the OSWESTRY Disability Index questionnaire only for lumbar patients (Supplementary Tables S2 and S3). In the prospective study, patients completed the questionnaires at several pre-determined follow-up

intervals: before treatment, and then at 1, 3, and 6 months post-treatment. In the present retrospective study, an analysis of the patients' medical records was conducted to collect additional long-term data. According to the criteria published by Oder et al. in 2008 [29], pain reduction on the NRS scale was classified as excellent (score 0–3), moderate (3.1–6.5), and ineffective (6.6–10). Additionally, the number of patients who demonstrated the minimal clinically important change (MCIC) for the PROs was also calculated [30–32]. Furthermore, we also intended to evaluate whether the patients received any other infiltration of PRGF or other type of treatment during this additional follow-up period.

### Sample Size and Statistical Analysis

The number of patients included in this study was the number of patients who completed the follow-up of the prospective study BTIIMD_02_EP/20/DISC who gave their informed consent and met the inclusion and exclusion criteria. Specifically, 32 patients completed the follow-up of that study [22], so this would be the maximum number of patients included in the present retrospective study. In addition, we conducted a post hoc power analysis using the obtained sample and effect size, and a $p$ value of 0.05.

Descriptive data were presented as frequencies and percentages. The results of the outcome measures were reported as median and interquartile ranges. All data values were subjected to a normality test using the Shapiro–Wilk test. The Friedman test with Dunn's multiple comparisons test was applied to assess changes in outcome measures between pre- and post-treatment. Analysis of categorical data (classification of treatment success) was carried out with the chi-square test. Statistical significance between groups was accepted for $p$ values lower than 0.05. Statistical analyses were performed with SPSS software (version 23; IBM, Chicago, IL, USA).

## RESULTS

### Characteristics of Patients and PRGF

The 6-month follow-up of the prospective study (BTIIMD_02_EP/20/DISC) was completed by 32 patients. The present retrospective study aimed to obtain data from these patients. We were able to secure data from 27 of the 32 patients (84.3%), as no additional information was available from five patients (Table 1).

Thus, the study participants were 40.7% female, with a mean age at baseline of 54.9 ± 10.1 years and a mean body mass index of 25.2 ± 3.1. The median duration of pain evolution prior to treatment was 4 months, while the median patient follow-up was 24 months after the treatment. Regarding the etiology of the pain (questions 2a and 2a of the COMI questionnaire), 18 patients (66.7%) exhibited pain predominantly of a back origin, 6 patients (22.2%) demonstrated pain of a radicular nature, and three patients (11.1%) exhibited a combination of both. A total of 52 intervertebral discs were infiltrated in the 27 patients, the majority of these procedures being conducted at the lumbar region (92.6%). The most prevalent radiological finding on MRI was Pfirrmann [33] grade III (42.3%), followed by grade V (26.9%). Most patients (66.7%) received two series of infiltrations, while 33.3% received three. Regarding the number of infiltrated levels, 55.6% of patients underwent treatment on two levels, 25.9% on one level, and only 18.5% were treated on three levels. When considering specific levels, the highest proportion of infiltrations were conducted at the lower lumbar region, specifically at the L5–S1 (40.4%) and L4–L5 (38.5%) levels (Table 1).

The characteristics of the PRGF infiltrated in the 27 patients were as follows: 463 ± 134 ($\times 10^3$/µl) platelets, 0.01 ± 0.01 ($\times 10^6$/µl) erythrocytes, and 0.27 ± 0.19 ($\times 10^3$/µl) leukocytes. The mean increase of platelets in PRGF over the peripheral blood value was 2.2 ± 0.4.

**Table 1** Baseline and demographic characteristics of the patients included in the retrospective study

| | |
|---|---|
| Patients (*n*) | 27 |
| Gender | |
| Female (*n*, %) | 11 (40.7%) |
| Male (*n*, %) | 16 (59.3%) |
| Age (years, mean ± SD) | 54.4 ± 10.1 |
| Height (cm, mean ± SD) | 171.0 ± 7.0 |
| Weight (kg, mean ± SD) | 73.9 ± 12.0 |
| Body mass index (kg/m$^2$, mean ± SD) | 25.2 ± 3.1 |
| Pain evolution period (months, median [IQR]) | 4 [3–6] |
| Follow-up period (months, median [IQR]) | 24 [22–28] |
| Sector of the column | |
| Lumbar (patients, *n*, %) | 25 (92.6%) |
| Cervical (patients, *n*, %) | 2 (7.4%) |
| Intervertebral discs (*n*) | 52 |
| MRI Pfirrmann grade | |
| II (discs, *n*, %) | 7 (13.5%) |
| III (discs, *n*, %) | 22 (42.3%) |
| IV (discs, *n*, %) | 9 (17.3%) |
| V (discs, *n*, %) | 14 (26.9%) |
| Series of infiltration | |
| Two series (*n*, %) | 18 (66.7%) |
| Three series (*n*, %) | 9 (33.3%) |
| Multiple levels injected | |
| One level (*n*, %) | 7 (25.9%) |
| Two levels (*n*, %) | 15 (55.6%) |
| Three levels (*n*, %) | 5 (18.5%) |
| Levels infiltrated | |
| C5–C6 (*n*, %) | 2 (3.8%) |
| C6–C7 (*n*, %) | 1 (1.9%) |
| L2–L3 (*n*, %) | 2 (3.8%) |
| L3–L4 (*n*, %) | 6 (11.5%) |
| L4–L5 (*n*, %) | 20 (38.5%) |
| L5–S1 (*n*, %) | 21 (40.4%) |

*IQR* interquartile range, *MRI* magnetic resonance imaging

## Analysis of Clinical Outcomes

The COMI and ODI questionnaires were used to evaluate the efficacy of PRGF infiltrations. Overall, the clinical and functional improvements obtained at the 6-month follow-up in the prospective study were maintained at 24 months, exhibiting statistically significant results ($p<0.001$) with respect to baseline (Fig. 1 and Table 2).

NRS pain (COMI pain score) was significantly reduced after PRGF treatment from 8.0 [6.0–9.0] to 2.0 [0.0–3.0] at 6 months. This improvement was maintained at 24 months (2.0 [1.0–3.0]) with a median similar to that at 6 months. As with pain levels, the COMI disability score demonstrated a statistically significant improvement at the 6-month follow-up (from 2.5 [1.3–5.0] to 0.0 [0.0–0.0]), which was also maintained at the 24-month assessment (0.0 [0.0–0.0]). The COMI total score exhibited a similar pattern to that observed in the previously described analyses, remaining below 1 point at both the 6- and 24-month time points (0.9 [0.0–2.6] and 0.7 [0.2–1.8], respectively). Finally, the Oswestry Disability Index (ODI) also demonstrated a statistically significant reduction at the 6-month post-treatment follow-up, with a mean score of 9 [1–16], indicating a notable improvement from the initial 38 [28–52]. This favorable outcome was sustained at the 24-month time point, exhibiting even more pronounced benefits compared with the 6-month findings (4 [0–6]). While the improvement in the ODI scale values at 24 months did not reach statistical significance when compared to the 6-month data ($p=0.609$), it did achieve a statistically significant improvement when evaluated against the baseline values ($p<0.001$) (Table 2). A post hoc power analysis of the pre- and post-treatment comparison showed

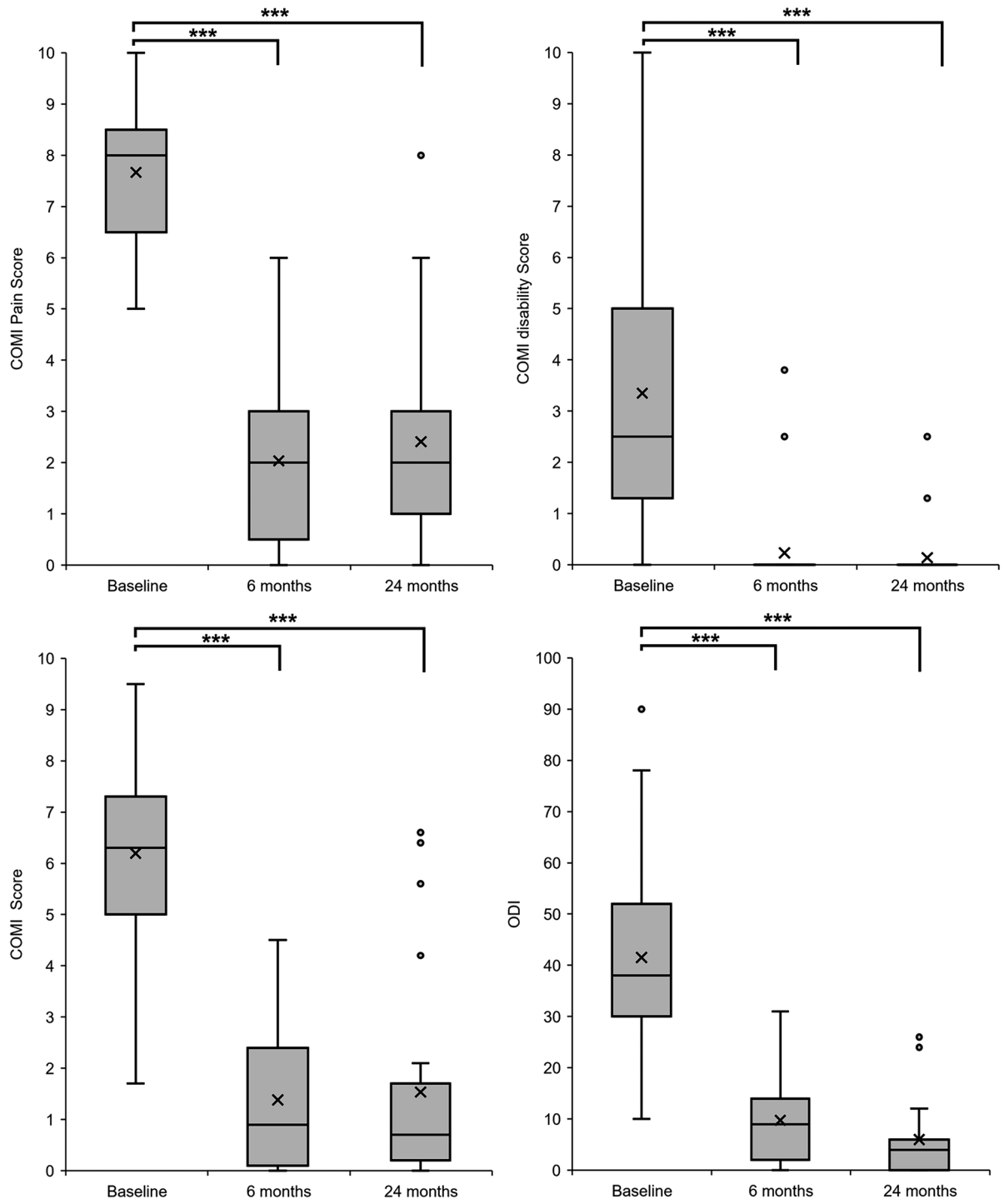



**Fig. 1** Clinical outcomes for the patients included in this retrospective study. COMI Pain Score (NRS), COMI Disability Score, and COMI total score are shown for all patients ($n = 27$) while the Oswestry Disability Index only for lumbar cases ($n = 25$). Median values are shown by a *horizontal line* and mean with a *cross*. First and third quartiles (25th and 75th percentiles) are represented by the lower and upper limits of the box, respectively. The 2.5th and the 97.5th percentiles are shown as the lower and upper whiskers, respectively. The outliers are represented as *dots*. *** indicates $p < 0.001$

**Table 2** Evaluation of outcomes before treatment (baseline) and after 6 and 24 months of follow-up ($n = 27$)

| Outcome variable | Median [IQR] | *p* value vs. basal | *p* value vs. 6 months |
|---|---|---|---|
| COMI pain score (NRS) | | | |
| Basal | 8.0 [6.0–9.0] | | |
| 6 months | 2.0 [0.0–3.0] | **< 0.001** | |
| 24 months | 2.0 [1.0–3.0] | **< 0.001** | > 0.999 |
| COMI Disability score | | | |
| Basal | 2.5 [1.3–5.0] | | |
| 6 months | 0.0 [0.0–0.0] | **< 0.001** | |
| 24 months | 0.0 [0.0–0.0] | **< 0.001** | > 0.999 |
| COMI total score | | | |
| Basal | 6.3 [4.8–7.3] | | |
| 6 months | 0.9 [0.0–2.6] | **< 0.001** | |
| 24 months | 0.7 [0.2–1.8] | **< 0.001** | > 0.999 |
| Oswestry Disability Index | | | |
| Basal | 38 [28–52] | | |
| 6 months | 9 [1–16] | **< 0.001** | |
| 24 months | 4 [0–6] | **< 0.001** | 0.609 |

Results are presented as median [IQR]

*IQR* interquartile range, *COMI* core outcome measure index, *NRS* numeric pain rating scale

Statistically significant differences ($p < 0.05$) according to Friedman's test with Dunn's multiple comparison test are shown in bold. Oswestry Disability Index only for patients with low back pain ($n = 25$)

a power of 100% at a significance level of 0.05 given a sample size of 27 patients.

The data obtained are additionally represented in Fig. 2, with consideration given to the time series, which illustrates a sustained reduction in scores at 24 months across the four scales.

The efficacy of the treatment can be classified according to the reduction in pain [29]. At the 24-month period, the number of patients with a pain level lower than 3 (excellent response) was maintained. Furthermore, the reduction in pain was considered excellent in 22 out of 27 patients (81.5%) at both 6 and 24 months after treatment (Fig. 3). However, between 6 and 24 months of follow-up, we reduced the number of patients with moderate treatment success from 18.5 to 7.4%. These three patients (11.1%) who change category worsened from moderately effective treatment at 6 months to ineffective treatment at 24 months after the end of PRGF infiltrations (Fig. 3). No statistically significant differences were found between treatment success at 6 and 24 months ($p > 0.05$).

Focusing on the changes in the pain scale before treatment and at the end of the follow-up period (median 24 months) (Δ basal-final), we observed (Fig. 4) that 24 of the 27 patients (89%) exhibited positive values in the pain difference, indicating that their final pain level was less than their pre-treatment level. Two patients (7%) showed no change and only one patient (4%) experienced an increase in pain relative to the baseline value (red dot

in Fig. 4). Among the patients who demonstrated improvement, 22 of them, 81.5% of the total (green dots in Fig. 3) met the criteria for a minimally relevant clinical improvement (MCIC), defined as a minimum of a three-point improvement on the pain scale (threshold of the dashed black line). Gray dots indicate patients who exhibited no change in pain status following PRGF infiltration, or showed improvement, but this improvement did not exceed the MCIC threshold (black dotted line). Supplementary Figures S1 to S7 show the stratified data by sex, age, and column sector. No differences were found according to these variables because almost all patients had a positive outcome and stratification reduced the N.

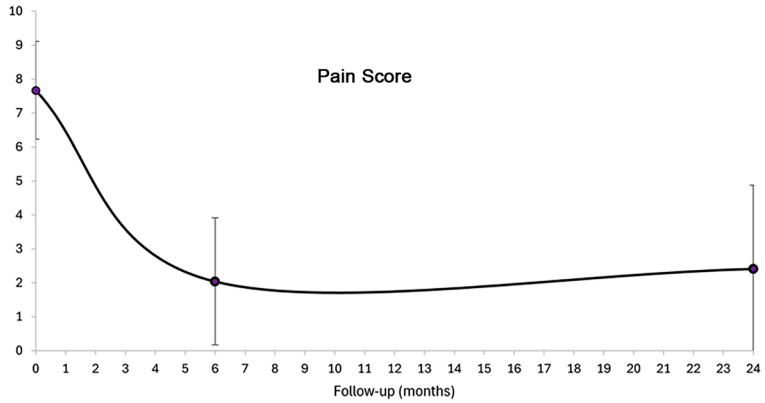
Regarding the MCIC values obtained for all the parameters analyzed, it was observed that the reduction of pain greater than 30% (MCIC) was achieved by a similar number of patients at 6 and 24 months, 24 (89%) and 22 (82%) patients, respectively. In the COMI score the data were also in this same line, as there was no difference between MCIC (≥ 2.2 points) at 6 and 24 months, achieved by 24 of the 27 patients (89%). Similarly, the percentage of patients achieving MCIC on the Oswestry scale was exactly the same at 6 and 24 months, 23 of the 27 patients (92%) obtained differences of at least 10 points on this scale. The results were found to be statistically non-significant ($p > 0.05$).

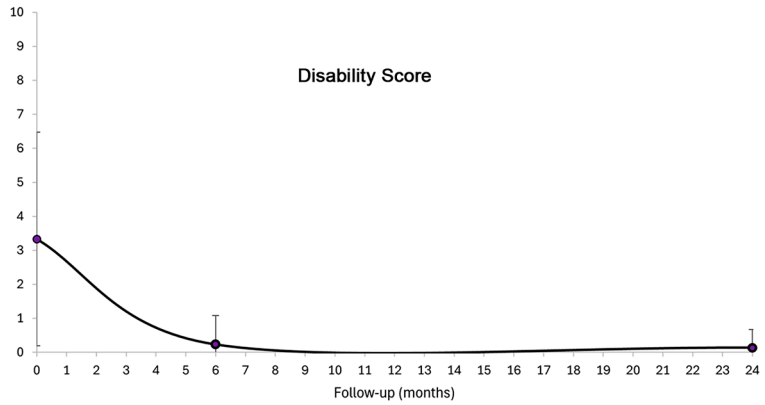
Additionally, data were collected on other treatments that the patients may have undergone. No invasive procedures, such as surgery, were conducted on any of the patients for the treatment of back pain. No corticosteroids or anesthetics were infiltrated. However, it was noted that ten out of the 27 patients (37%) received additional PRGF treatment. Among these, nine patients received one additional PRGF booster infiltration, while one patient received two. Furthermore, six out of the 27 patients (22%) were engaged in regular physiotherapy.

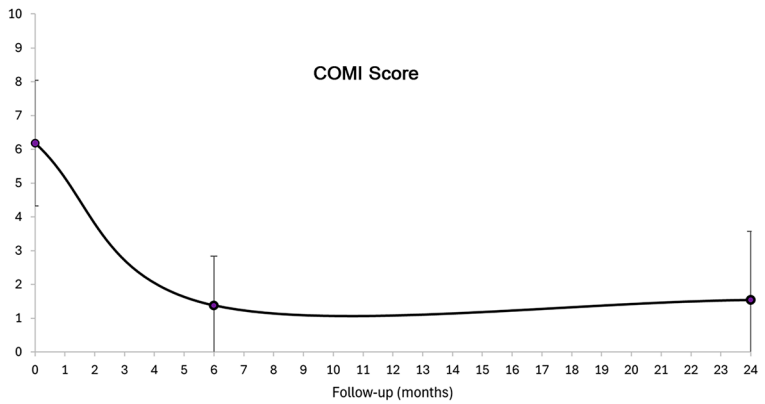
## DISCUSSION

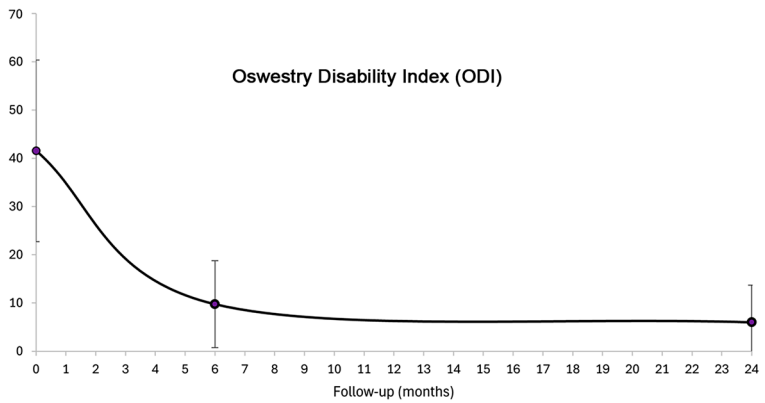
In previous studies, the intradiscal and epidural infiltration of PRGF has been demonstrated to markedly diminish chronic back pain and physical disability for a minimum of 6 months [19, 22]. The current study lends support to the findings obtained in the previous prospective study [22], providing additional data on the long-term effects since the improvement in these parameters was maintained in the majority of patients (85.2%) over a median follow-up period of 24 months. Thus, the COMI Pain score remains at the same median and the COMI Disability score exhibits consistent results, indicating a non-disability status with a value of 0 in both follow-up periods of 6 and 24 months. The COMI total score showed a change from a median of 0.9 at the 6-month follow-up to a median of 0.7 at 24 months. Nevertheless, the Oswestry Disability Index revealed a reduction of five points between the 6- and 24-month periods, which is considered a significant improvement, but it did not achieve the MCIC of 10 points deemed clinically meaningful for this assessment scale [32].

There are a few studies that have evaluated the long-term effectiveness of PRP, but those that have done so have obtained results that are consistent with our findings. Thus, Akeda et al. [34] conducted a follow-up study of 11 patients who had previously received PRP treatment for low back pain of discogenic origin. Their findings indicated that the clinically significant improvement in treatment outcomes was sustained in 91% of patients for an average of 5.9 years of follow-up. In another prospective cohort study, Cheng et al. [35] examined the long-term outcomes of 19 patients who had previously undergone intradiscal infiltration with 3–4 ml of PRP at 2–3 lumbar levels. The mean follow-up period was 6.6 years, during which time a clinically significant reduction in pain and an improvement in function was also maintained. A review of studies with a follow-up period similar to ours identified the studies by Monfett et al. [36] and Williams et al. [37], which also observed the long-term maintenance of pain reduction and improved function at 2 years of follow-up. In the first of the aforementioned studies, a clinically


Pain Score
Follow-up (months)


Disability Score
Follow-up (months)


COMI Score
Follow-up (months)


Oswestry Disability Index (ODI)
Follow-up (months)

◂**Fig. 2** Representation of the results of the questionnaires as a time series, before treatment (time 0), and at 6 and 24 months after the end of treatment. The mean ± standard deviation is plotted for each point

meaningful and sustained improvement was observed 2 years of post-PRP injection in 21 patients with low back pain, for worst pain NRS, function as assessed by the Functional Rating Index (FRI), and pain and function as evaluated by SF-36 [36]. The second study examined a cohort of patients whose neck pain was treated with heterogeneous blood derivatives based on an infiltration of the whole functional spinal unit (FSU) [37]. As observed in previous studies, they also demonstrated sustained pain reduction and improved function. However, in contrast to our study, Williams et al. reported two moderate adverse reactions among the 14 patients of the study [37]. In a recent study, Barbieri and colleagues [38] evaluated the efficacy of PRGF in a cohort of 32 patients with back pain due to multiple causes. However, in contrast to our study, they observed clinical improvement in a smaller subset of patients (27%). This discrepancy may be attributed to variations in the inclusion and exclusion criteria. In our study, all patients exhibited disc degeneration as determined by magnetic resonance imaging (MRI). In contrast, the Barbieri study population was more heterogeneous, comprising individuals with pain attributed to degenerative disc disease, facet joint arthrosis, sacroiliac pain, central canal narrowing, or foraminal stenosis. It is possible that other factors, such as the number of infiltrations and the volume of PRGF infiltrated in each structure, may have also contributed to this difference.

Nowadays, the maintenance of functionality and the reduction of back pain throughout a person's lifetime represents a significant challenge. It has been observed that the majority of episodes of back pain are of short duration; however, recurrent episodes can become frequent.

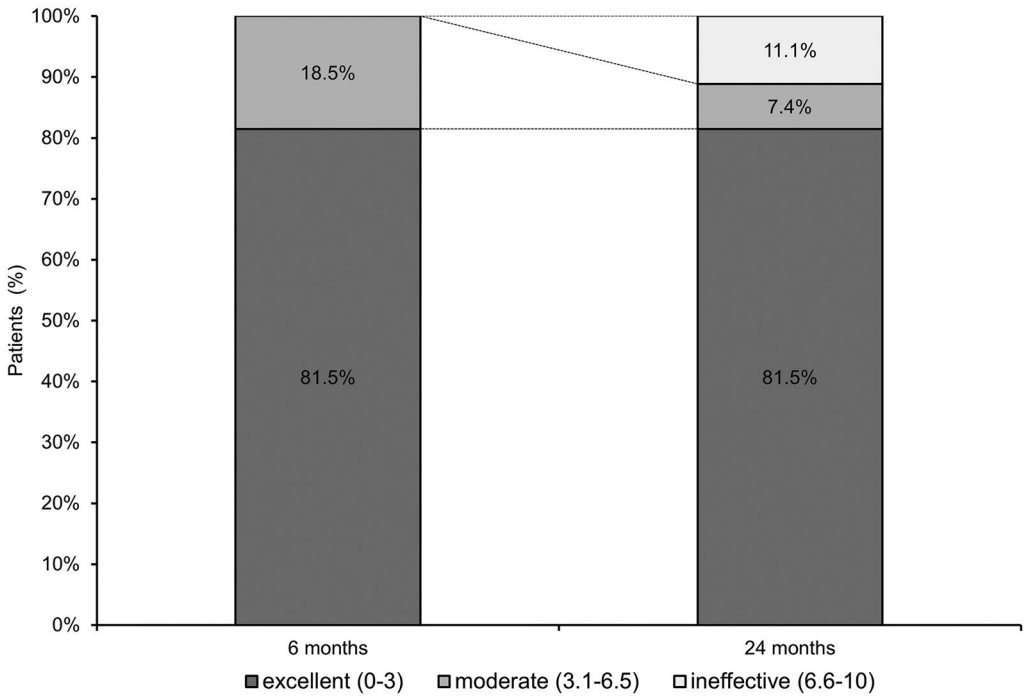



**Fig. 3** Representation of treatment response in terms of pain reduction during follow-up. This reduction was classified as excellent (score 0–3 on the NRS pain scale), moderate (NRS 3.1–6.5) and ineffective (NRS 6.6–10). The proportion of patients falling into each category is indicated

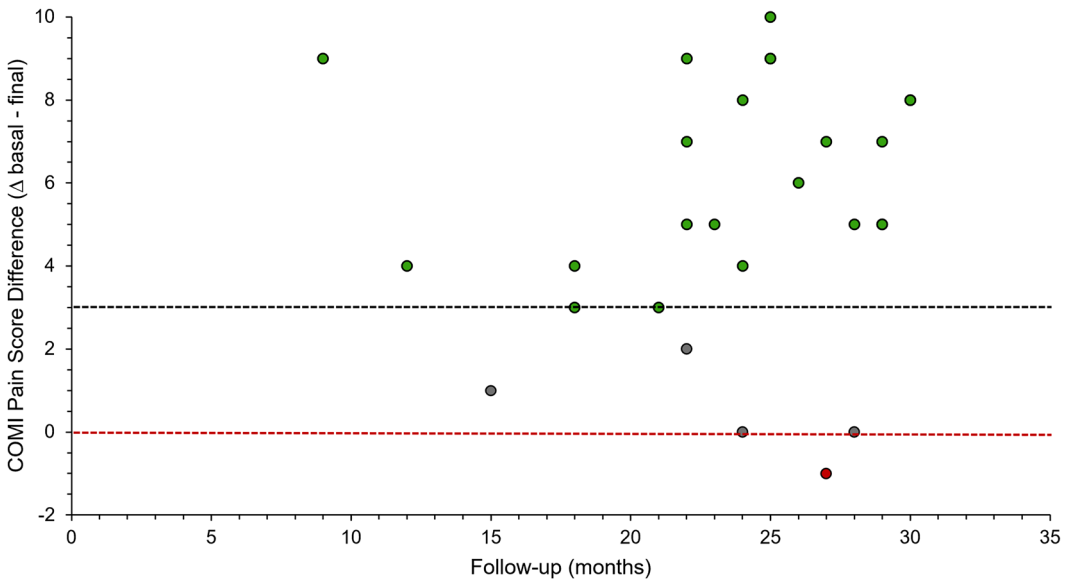



**Fig. 4** Graph illustrating the improvement in pain scale scores over time for the 27 patients included in the study COMI Pain Score Difference (Δ basal- final). Each patient is represented by a single data point. Twenty-two patients exhibited an improvement in their condition as a result of the treatment, exceeding the minimal clinically important change (MCIC) threshold for pain (demonstrated by *green dots* above the *dashed black line*). The *grey dots* represent patients who showed improvement but did not reach the MCIC threshold (*dashed black line*), or who remained at the same level as at the beginning of treatment (*dashed red line*). One patient (*red dot*) evidenced a worsening of their condition in comparison to their baseline situation, with a value below the *red dashed line*

The concept of back pain as a long-term condition with a variable course is now widely accepted as a more accurate understanding of this condition than the previous notion of unrelated episodes [4]. It is thus essential to include minimally invasive treatments such as PRGF in the therapeutic arsenal to address this unmet medical need and, consequently, to reduce the recurrence of back pain throughout the patient's lifespan. The responder rate in our study was 85.2%, as four of the 27 patients (14.8%) failed to achieve the minimum clinically significant difference in pain at the 24-month follow-up. This percentage is noteworthy in light of a review of the literature indicating that approximately 33–69% of individuals with back pain report a recurrence within 1 year after recovering from a previous episode [26, 39]. In any case, back pain is a complex and multifactorial condition that requires a multidisciplinary approach to treatment with the initial focus being the elimination of factors that contribute to its development. This may include the modification of lifestyle habits that contribute to the condition, such as maintaining uncomfortable postures, excessive loads, or prolonged periods of sitting [39]. In addition to lifestyle factors, it is important to consider the role of psychological and social factors, comorbidities, and other pain-processing mechanisms in the development of this pathology [4, 6, 40, 41].

One of the primary causes of back pain is the degeneration of the intervertebral discs and associated tissues, which is a common process that occurs with age or following an injury [42, 43]. The underlying molecular mechanism by which PRP exerts an analgesic effect in pathologies of the musculoskeletal system remains poorly understood. A growing body of evidence suggests that there is a dual behavior in the immediate and sustained release of multiple growth factors with neuroimmunomodulatory effects, including TGF-β, HGF, and IGF-1 [13, 44]. These growth factors and other plasma and platelet pool growth factors and other biomolecules are conveyed into the pathological tissue by another

component of the PRGF, namely the fibrin, which acts as an autologous biomimetic scaffold [13, 14]. Additional mechanisms contributing to the efficacy of PRP may include the inhibition of the NF-kB signaling pathway, blockade of IL-1 receptors, polarization of macrophages towards trophic M2, increasing the expression of molecules involved in disc homeostasis, such as the semaphorin Sema3A, and activation of endocannabinoid-mediated pathways, as previously described [45–49]. However, it should be noted that not all PRP formulations have demonstrated the same results, due likely to the different composition of leukocytes, erythrocytes and platelets in PRP. One of the main areas of controversy is the inclusion of leukocytes in PRP, as several studies have demonstrated that leukocytes can have a detrimental effect on the intervertebral disc [46, 50, 51]. PRGF is a formulation with a moderate concentration of platelets and an almost total absence of leukocytes [24]. The coding data, according to the Consensus Expert's classification and coding demonstrated that in all cases the second and third digits of the code of the PRGF of the patients were 00, indicative of the absence of erythrocytes and leukocytes, respectively [52, 53].

However, this study is not without limitations. The first limitation is intrinsic to the nature of the study design, which is a retrospective observational study in which follow-up was not conducted at a fixed point in time. Our follow-up had a mean of 24 months with an IQR between 22 and 28. The second limitation to be considered is the absence of images that seek to correlate the observed clinical improvement with the potential structural changes that may have occurred within the intervertebral disc. A third limitation is the low number of patients with cervical pain, as observed in the previous prospective study. Finally, a fourth limitation is the absence of a control or sham group.

## CONCLUSIONS

The results of this retrospective study demonstrate that treatment of chronic back pain with PRGF was effective in maintaining pain reduction and improving function for at least 24 months after treatment. The high response rate of more than 85% of patients encourages further randomized clinical trials to confirm these findings.

## ACKNOWLEDGEMENTS

We thank the participants of the study

***Author Contributions.*** All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Eduardo Anitua, Isidro Milani, Àlex Martínez, Freddy Cabello, Roberto Prado, Sabino Padilla, and Luis Sanado. The first draft of the manuscript was written by Roberto Prado, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

***Funding.*** No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Declarations*

***Conflict of Interest.*** The authors declare that Eduardo Anitua is the Scientific Director of, and Sabino Padilla and Roberto Prado are scientists at the BTI—Biotechnology Institute I MAS D, a biomedical company that investigates the fields of re-generative medicine and PRGF-Endoret technology. Isidro Milani has nothing to disclose. Àlex Martínez has nothing to

disclose. Freddy Cabello has nothing to disclose. Luis Sanado has nothing to disclose.

***Ethical Approval.*** The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of CEIm-E (protocol code BTIIMD-01-ER-24-DISC2). Informed consent was obtained from all subjects involved in the study.



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