Current Pain and Headache Reports (2019) 23: 20
https://doi.org/10.1007/s11916-019-0758-0

OTHER PAIN (A. KAYE AND N. VADIVELU, SECTION EDITORS)

Regenerative Techniques for Neuraxial Back Pain: a Systematic Review

Ali K. Valimahomed[1] · Paul Ryan Haffey[2] · Richard D. Urman[1] · Alan D. Kaye[3] · R. Jason Yong[1]

Published online: 11 March 2019

Abstract

Purpose of Review Regenerative modalities have been identified in numerous clinical studies as beneficial in various settings. The focus of this review is to summarize key studies and current concepts for the role of regenerative medicine in the treatment of neuraxial back pain.

Recent Findings Recent studies have demonstrated the benefit of regenerative therapies for the treatment of neuraxial back pain. A literature review of clinical trials published between 2015 and 2017 was performed using OVID, PubMed, and Google Scholar to identify investigations attempting to determine the efficacy of various regenerative modalities on two primary sources of low back pain: facet arthropathy and degenerative disc disease. The seven articles analyzed in this systematic review present promising data regarding the use of these autologous biologic treatments, but many of these investigations have several limitations in common including small sample size.

Summary Regenerative medicine has been shown to demonstrate efficacy in the treatment of neuraxial back pain. As the field advances, new studies are needed comparing efficacy and safety profiles to better determine best practice techniques and standards in the future.

Keywords Regenerative · Biologics · Back pain · Neuraxial · Medicine · Treatment

Introduction

In a large-scale analysis surveying the 20.1 million Americans who have reported work disability, 30.3% state that their disability was a function of back or neck problems [1]. For patients 45–65 years of age, low back pain (LBP) is the number 1 cause of disability and those annual costs associated with LBP exceed $100 billion. [2••]. The financial burden imposed by LBP to patients, physicians, and the economy has prompted extensive research aimed at ameliorating the effects of the epidemic of LBP.

LBP is commonly attributed to pathology at the zygopophysial (facet) joint or the intervertebral disc. Degeneration of the intervertebral disc is a significant contributor to low back pain and radiculopathy. This process is physiologic and may start as early as 2 years of age. The intervertebral disc is the major shock absorbing point of the spine that is comprised of inner and outer portions: the nucleus pulposus and the annulus fibrosis, respectively. Degeneration of either of these structures can result in LBP and/or compression of surrounding nerve structures, resulting in radiculopathy [3••, 4, 5••]. The facet joints, like other major joints in the body, are synovial joints. They possess a fibrous capsule enshrouding the joint, articular cartilage, fat containing pouches at their superior and inferior aspects, and a synovial membrane [6••]. Breakdown of these structures, just as in the knee or hip, results in pain and loss of function.

At the forefront of research into resolving LBP are regenerative procedures using autologous biologic injectates.

This article is part of the Topical Collection on *Other Pain*

✉ Richard D. Urman
rurman@bwh.harvard.edu

[1] Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

[2] Department of Physical Medicine and Rehabilitation, New York Presbyterian Hospital, Weill Cornell Medical College/Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

[3] Department of Anesthesiology, Louisiana State University Health Sciences Center, New Orleans, LA, USA

Platelet-rich plasma (PRP) is one such product created by taking blood from a patient and extracting the platelet containing plasma via centrifugation. The PRP contains growth factors that include transforming growth factor-β, platelet-derived growth factor, insulin-like growth factors I and II, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, and endothelial cell growth factor. These growth factors have the potential to heal damaged tissue or allow for new tissue formation [7]. Recent studies suggest that PRP may have a role in treating LBP. Injecting these healing/growth factors directly into the affected area may potentially allow for regeneration of either cartilage or the nucleus pulposus.

The most controversial of the regenerative modalities is the use of mesenchymal stem cells (MSC). Unfortunately, some physicians have irresponsibly and erroneously marketed stem cell therapy as a "cure all" to patients without scientific evidence to support the claim and without educating patients on the experimental nature of the treatment. In a recent perspective piece published in the New England Journal of Medicine, Drs. Charo and Sipp discuss many of the predatory practices employed by some physicians using stem cells. These practices have become so extreme that they have led to blindness, paralysis, and even death [8]. Although MSCS procedures can be quite lucrative, it is our duty to uphold the Hippocratic oath; first do no harm, and critically analyze the current body evidence in order to drive safe medical practices. With that said, there may be a place for the use of MSC with the aim of relieving LBP.

Several researchers are investigating the efficacy of MSC injections to regenerate discs affected by degenerative disc disease and the cartilage that relieves friction between the facet joints of the spine. Physicians utilize MSCs derived from the patient's own bone marrow aspirate or adipose cells. These MSCs are theoretically capable of initiating cell-to-cell interactions that may aid in the regeneration of cartilage. One specific factor present in MSCs, transforming growth factor-beta (TGF-B), may have the ability to potentiate the proliferation of chondrogenic cells. These cells could, theoretically, regenerate cartilage and/or differentiate into cells similar to the nucleus pulposus [9]. If effective, injections of MSCs could have a major impact on the phenomenon of back pain.

Additional regenerative procedures using autologous injectate are also being investigated for potential use in the relief of LBP. Stromal vascular fraction (SVF) is similar to the MSCs that are aspirated from adipose, but employs a specific kit to isolate the MSCs and other growth factors [10]. Similarly, platelet lysate (PL) is created by lysing platelets and eliminating the excess cellular material to isolate a growth factor concentrate for injection [11]. This review aims to objectively evaluate some of the most innovative regenerative modalities being investigated today in the treatment of low back pain.

Methods

Items were selected utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). http://www.prisma-statement.org guideline as outlined in Fig. 1. We conducted a literature review of clinical trials published between 2015 and 2017 that was performed using OVID, PubMed, and Google Scholar to identify investigations attempting to determine the efficacy of various regenerative modalities on two primary sources of low back pain (LBP): facet arthropathy and degenerative disc disease. The present investigation used various iterations of the following search terms during literature review: "regenerative medicine," "low back pain," "degenerative disc disease," "mesenchymal stem cells," "platelet-rich plasma," and "facet arthropathy." A total of 297 articles were identified; 35 duplicates were excluded from initial review. Then, 233 articles were excluded, as they fell outside of the date parameters we had established, they were international publications, or they utilized modalities outside of the scope of this review. Finally, 29 articles were then reviewed, 22 of which were excluded because they did not target the intervertebral disc or facet joint and/or did not utilize outcome measures we deemed relevant to current practice. A total of eight articles were selected for inclusion in the manuscript after meeting our criteria (Table 1). We sought to include recent studies spanning the years 2015–2017 that were published in the USA; however, we did include two internationally published studies due to the lack of sufficient regenerative work aimed at facet-mediated pain in taking place in the USA. Articles were then divided into two groups based on the pathology each regenerative procedure sought to treat: discogenic/radicular and facet-mediated back pain.

Results Discogenic/Radicular Pain

Of the articles aimed at ameliorating LBP related to disc-related pathology using PL, Centeno et al. [13] had the largest sample size ($n = 470$). In this prospective cohort trial, patient data was extrapolated from a patient registry database comprised of 20 physicians practicing at 13 outpatient clinics in the USA receiving PL injections into the epidural space. Inclusion criteria was comprised of patients with complaints of LBP manifesting symptoms consistent with radiculopathy diagnosed based on history, physical exam findings, and MRI studies demonstrating pathology that correlated with clinical presentation. The mean patient age was 53.6 years of age. Patients with coagulopathy, local infection, septicemia, pregnancy, or neurological disorders at the time of the study were excluded from participation. Interestingly, no commercial kit was utilized to extract the platelet lysate; instead, whole blood was prepped via centrifugation, freezing, thawing, followed by re-centrifugation. Patients received a transforaminal or

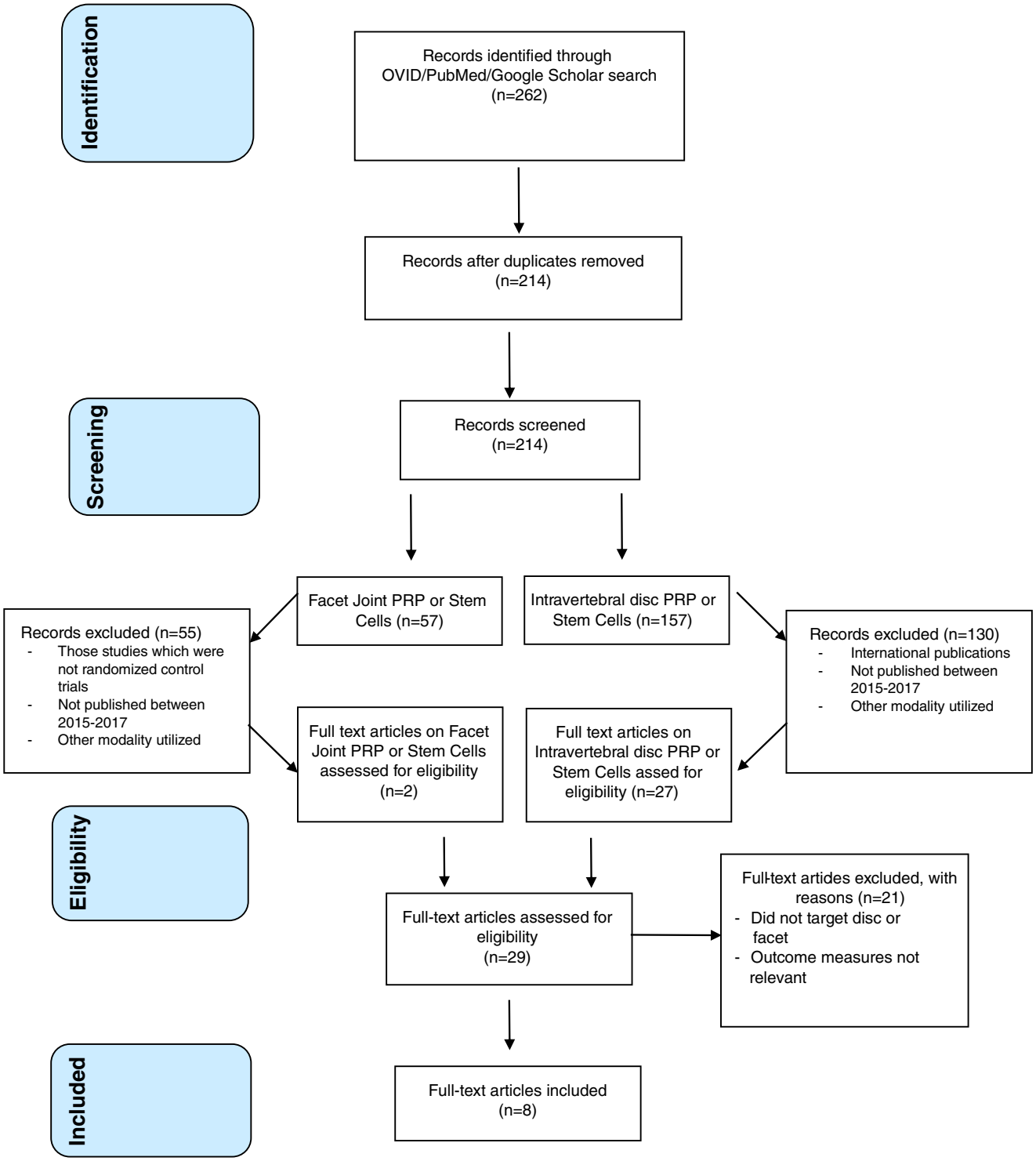

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart

interlaminar epidural injection utilizing C-arm fluoroscopy guidance with confirmation established via radiographic contrast injection. Final injectate consisted of PL 50% by volume, 4% lidocaine at 25% by volume, and compounded preservative free 100–200 ng/mL hydrocortisone (obtained via different compounding pharmacies) at 25% by volume. For transforaminal and interlaminar injections, 3–5-cm^3 volume was injected. Injection timing and frequency was not controlled for in this investigation. Patients reported statistically significant improvements based on numeric pain score (NPS) and functional rating index (FRI) change scores at all follow-up intervals; modified Single Assessment Numeric Evaluation

Table 1 Biologics for neuraxial pain

Author, year	Study format	Biologic agent	Location treated	No. of patients	Age range	Follow-up	Outcome measures	Results	Adverse events	Preop antibiotics
Tuaki-Wosornu et al., 2016	Prospective, double--blind RCT	PRP	Intradiscal	47	Mean age treatment group 41 Mean age control group 44	1 week, 4 weeks, 8 weeks, 6 months, 1 year	Functional rating index (FRI), numeric rating scale (NRS) for pain, the pain and physical function domains of the 36-item Short Form Health Survey, and the modified North American Spine Society (NASS) Outcome Questionnaire	Participants who received intradiskal PRP experienced significantly greater improvements in FRI, NRSeBest Pain, and NASS satisfaction scores compared with those who received contrast agent alone over 8 weeks. Additionally, the significant improvement in FRI score was sustained for up to 1 year or more after PRP injection.	No	1 g Cefazolin
Comella et al., 2016	Open-label trial	Stromal vascular fraction plus PRP	Intradiscal	15	Mean age 51.5	2 months, 6 months	Visual analog score (VAS), present pain index (PPI), and minimum, maximum, and current pain ratings; Beck Depression Inventory (BDI), Oswestry Disability Index (ODI), Short Form McGill Pain Questionnaire (SM-MPQ), Short Form 12 (SF-12), and the Dallas Pain Questionnaire	Patients demonstrated improvement with flexion over 6 months, VAS scores improved from an average of 5.6 to 3.6, PPI scores improved from an average of 2.6 to 1.8, but demonstrated a slight increase in anxiety/depression and reduction in social interest; patients also reported a significant improvement in SF12-PCs at 6 months	No	No
Cuellar et al., 2017	Prospective cohort	Autologous alpha-2--macroblobulin concentrate	Intradiscal	40 FAC-positive patients	Median age of 47.5	3 months and 6 months	ODI, VAS	Mean VAS improvement in FACT-positive patients was 4.9 ± 0.9 and 4.0 ± 1.0 at 3 and 6 months, compared to 1.5 ± 1.2 and 2.3 ± 1.3 in those with negative FACT ($p < 0.0001$); ODI improved on average 37 ± 9.3 and 28 ± 14 points at 3 and 6 months in FACT-positive patients compared to 9.4 ± 11.9 and 12.6 ± 11.8 points at 3 and 6 months in FACT-negative patients ($p < 0.0001$).	No	No
Pettine et al., 2015 [12]	Open-label trial	Bone marrow concentrate	Intradiscal	26	37.4–38	3 months, 6 months, 12 months	Magnetic resonance imaging scored according to the modified Pfirrmann scale, ODI, VAS	Patients receiving > 2000 CFU-F/mL experienced a significantly faster and greater reduction in ODI and VAS. Subjects > 40 years old	No	No

Table 1 (continued)

Author, year	Study format	Biologic agent	Location treated	No. of patients	Age range	Follow-up	Outcome measures	Results	Adverse events	Preop antibiotics
								who received < 2000 CFU-F/mL experienced an average pain reduction of 33.7% (ODI) and 29.1% (VAS) at 12 months, while all other patients' average reduction was 69.5% (ODI, p5.03) and 70.6% (VAS, p5.01).		
Centeno et al., 2017 [13]	Prospective cohort	Platelet lysate	Epidural	470	Mean age 53.6	1 month, 3 months, 6 months, 12 months, 18 months, 24 months	Numeric pain score (NPS), functional rating index (FRI), and a modified Single Assessment Numeric Evaluation (SANE) rating	Patients treated with PL epidurals reported significantly lower ($p < 0.0001$) NPS and FRI change scores at all time points compared to baseline. Post-treatment FRI change score means exceeded the minimal clinically important difference beyond 1 month. Average modified SANE ratings showed 49.7% improvement at 24 months post-treatment. Twenty-nine (6.3%) patients reported mild adverse events related to treatment.	Yes, 29; 26 pain, 3 with post-dural puncture pain—1 required autologous blood patch	No
Kirchner et al., 2016 [14]	Observational retrospective pilot study	Plasma rich in growth factors (PRGF)	One intradiscal, one intraarticular facet, and one transforaminal epidural injection	86	Median age: male 55, female 58	1 month, 3 months, 6 months	VAS over time	Pain reduction after the PRGF-Endoret injections showed a statistically significant drop from 8.4 ± 1.1 pre-treatment to 4 ± 2.6, 1.7 ± 2.3, and 0.8 ± 1.7 at 1, 3, and 6 months post-treatment, respectively, with respect to all the time evaluations ($p < 0.0001$) except 3 and 6 month whose significance was lower ($p < 0.05$). The analysis of the VAS over time showed that at 6 months, 91% of patients showed an excellent score, 8.1% showed a moderate improvement.	No	No
Wu et al., 2016 [15]		PRP	Lumbar facet joints	19	Mean age 52.53	1 week, 1 month,	VAS at rest and during flexion, Roland-Morris Disability	1 week post-treatment, low back pain reduced	4 pts. reported	No

Table 1 (continued)

Author, year	Study format	Biologic agent	Location treated	No. of patients	Age range	Follow-up	Outcome measures	Results	Adverse events	Preop antibiotics
	Prospective clinical evaluation					2 months, 3 months	Questionnaire (RMQ), ODI, and modified MacNab criteria for the pain relief	significantly compared with prior to treatment both at rest and during flexion. The outcomes were assessed as "good" or "excellent" for 9 patients (47.37%) immediately after treatment, 14 patients (73.68%) at 1 week, 15 patients (78.95%) at 1 month, 15 patients (78.95%) at 2 months, and 15 patients (78.95%) at 3 months. Statistically significant differences were observed based on RMQ and a more than 10% improvement in lumbar functional capacity was observed based on ODI between pre-treatment and post-treatment.	aggravation of LBP immediately post--treatment	
Aufiero et al., 2015 [18]	Single-center observational case series	PRP	Facet joints	5	Mean age 54.6	6 months, 12 months	VAS, perceived functional improvement	Case 1 60% symptom improvement following second injections, 100% improvement and return to sport at 6 months; Case 2: at least 30% symptom improvement following 1st injection, 60% improvement following the second series, and 1/10 VAS scale at 9 months; Case 3: at least 40% symptom improvement following 2nd injections, 2/10 VAS scale and improvement in functional status at 12 months; Case 4: 70% symptom improvement & increased functional status following 3rd injections; Case 5: 65–70% symptom improvement and increased functional status at 6-month follow-up. Patient reported reduced fear and anxiety over inciting events, improved	No	No

Table 1 (continued)

Author, year	Study format	Biologic agent	Location treated	No. of patients	Age range	Follow-up	Outcome measures	Results	Adverse events	Preop antibiotics
								sleep, and decreased pain medication use.		

(SANE) ratings averaged a 49.7% improvement at the final follow-up interval of 24 months. Of patients in the sample, 6.3% reported adverse events primarily comprised of pain. Of patients who had adverse events, 20.7% experienced symptoms consistent with dural tear, one of whom required treatment with an autologous blood patch.

Tuaki-Wosornu et al. [16] conducted a prospective double-blind randomized control trial that included 47 participants randomized to either receive intradiscal contrast or intradiscal PRP to determine the potential for PRP to decrease pain secondary to discogenic LBP. Patient's suffering from LBP for longer than 6 months after failure of conservative measures without contraindications who had preserved intervertebral disk height of at least 50%, MRI or CT scan findings demonstrating disk protrusion less than 5 mm, or presence of a grade 3 or 4 annular fissure as determined by discography were included in the trial. The mean age of the treatment group was 41, and the mean age of the control group was 44. Twenty-two patients were randomized to the control group, while 36 were randomized to the treatment group. To perform the procedure, a covered syringe containing 3–4 mL of PRP (treatment group) or contrast agent (control group) was prepared under a standardized protocol. Using fluoroscopic guidance, a 25-gauge spinal needle was advanced through a 20-gauge introducer needle into the mid-portion of the suspected disk levels, as well as into a control level, and the contents of the syringe were injected. If more than one disk was symptomatic with reproduction of concordant pain, the PRP or contrast was divided into equal doses and injected into each of the affected disks. Participants in the treatment group demonstrated statistically and clinically significant improvements in FRI, numeric rating score best pain (NRS), and North American Spine Society Outcome Questionnaire (NASS) patient satisfaction scores over 8 weeks compared with controls. Patients in the treatment group continued to report clinically significant improvements in FRI scores at 1-year follow-up evaluation. It is worth noting, however, that the clinically significant changes were observed only in worst pain scores and not in current or best pain scores. This represents a delta of 2.16, affirming a clinically significant change [17]. Also of note, 1-year follow-up data was reported to be clinically significant for ordinal, functional, and satisfaction scores. Conclusions cannot be drawn based on this information because of too few follow-up participants, who limit power.

Comella et al. [10] performed an open-label trial evaluating the efficacy of injecting intradiscal SVF plus PRP to potentially promote healing of the damaged intravertebral disc. Patients with evidence of degenerative disc disease (DJD) with LBP refractory to conservative treatment for longer than 6 months were considered eligible for participation. Aside from conventional selection criteria, patients without an intact annulus fibrosis were excluded due to inability to hold the implanted cell material. The mean age of patients was

51.5 years of age, and a total of 15 patients participated in the trial. Sixty milliliters of fat was collected from each patient, and the extracted material was prepared using an adipose SVF preparation kit and centrifuged per protocol. The final SVF preparation was then placed in 1–3 ccs of autologous PRP prepared by extracting autologous blood and centrifuging. Using fluoroscopic guidance and confirmatory contrast, 1 cc of the SVF/PRP injectate preparation was injected into the nuclei of the affected disc. If more than one disc was symptomatic, the SVF was divided and prepared with approximately 1 cc of PRP and subsequently injected into each affected disc. Outcome measures including range of motion, visual analog scale (VAS), present pain intensity (PPI), Oswestry Disability Index (ODI), Beck Depression Inventory (BDI), and Dallas Pain Questionnaire and Short Form (SF)-12 scores were followed at intervals of 2 and 6 months. Statistically significant improvements were observed in the following outcome measures: flexion, pain ratings, VAS, present pain intensity (PPI), and short form questionnaires. Improvements were reported in Dallas Pain Questionnaire scores, ODI, and BDI measures. VAS scores statistically improved from an average of 5.6 at baseline to 3.6 at 6 months ($p = 0.01$). This delta of 2.0 also represents a clinically significant change [17]. PPI scores statistically improved from an average of 2.6 at baseline to 1.8 at 6 months.

Pettine et al. [12] conducted an open-label pilot study that comprised of 26 patients who received intradiscal injections of autologous bone marrow concentrate to treat moderate to severe discogenic low back pain in an attempt to avoid or delay progression to lumbar fusion or artificial disc replacement. Patients who suffered from centralized LBP that was refractory to conservative management for at least 3 months, persisted for 6 months or greater, and demonstrated changes consistent with disc degeneration on MRI based on Pfirrmann scores of 4–7 were eligible for participation. The mean age ranged from 37.4 to 38 years of age. Sixty milliliters of bone marrow aspirate was extracted from the posterior iliac crest of each respective patient and processed according to protocol to yield a volume of 7 mL, 6 mL for injection and 1 mL for analysis—2–3 mL of injectate would be used for each symptomatic disc. Using fluoroscopic imaging to confirm placement of a 22-gauge needle, 13 patients subsequently underwent an intradiscal injection of autologous BMC at a single disc and 13 subjects had two adjacent symptomatic disc levels injected. Interestingly, an additional arm was incorporated into the study design allowing for patients with less than 25% improvement in ODI or VAS at or beyond the 6-month follow-up visit to receive a second BMC injection. Cellular analysis was performed on 20 out of 26 patient samples to determine total nucleated cell count and differentiation potential. Twelve-month follow-up MRI demonstrated an improvement of at least one Pfirrmann grade in five of ten one-level patients and three of ten two-level patients. All patients reported reduction in pain symptoms; those who received 2000 CFU-F/mL experienced a significantly faster and greater reduction in ODI and VAS scoring. Subjects older than 40 years who received fewer than 2000 CFU-F/mL experienced an average pain reduction of 33.7% (ODI) and 29.1% (VAS) at 12 months, while all other patients' average reduction was 69.5% (ODI, p5.03) and 70.6% (VAS, p5.01).

The use of biomarkers is a novel technique that may help to target regenerative therapies. In patients with DDD and radicular symptoms from the herniated nucleus pulpus (HNP), studies suggest that there is a positive predictive value for response to lumbar epidural steroid injection in patients where fibronectin-aggrecan complex (FAC), a by-product of cartilage degradation, is isolated in the epidural space. Working backwards, it has been postulated that an agent that inhibits the formation of FAC will be efficacious in the treatment LBP. Cuellar [22] performed a prospective cohort trial of 24 patients utilizing intradiscal autologous concentrated alpha-2-macroglobulin (A2M) injections to relieve LBP in patients with symptomatic degenerative disc disease (DDD) who tested positive for FAC. A2M is a protease inhibitor native to plasma that may help prevent the formation of FAC, which are synthesized with the help of proteases, and thus ameliorate LBP in patients with DDD. Patients with MRI findings consistent with Pfirrmann grade 2–4 degenerative disc disease at one or more level and axial LBP lasting for 6 months or longer with conservative management were eligible for participation in this trial. The median age of participants was 47.5 years of age.

Facet-Mediated Low Back Pain

The second group was comprised of regenerative procedures targeting facet-mediated LBP. Wu et al. [15] conducted a prospective clinical evaluation to determine the efficacy of PRP to combat LBP caused by facet arthropathy. Nineteen patients were enrolled in the study with an average age of 52.53 years. Participants were considered eligible if they were diagnosed with facet joint syndrome based on imaging modalities, including lumbosacral radiographs demonstrating signs consistent with facet joint syndrome, continuous or intermittent LBP, increased pain with flexion, rotation, lateral bending, fracture like feeling when bending down, experience of hard physical labor or sedentariness, and lack of neurological deficit. Autologous peripheral blood was taken from each patient and prepared per protocol resulting in a sample of 1–2 mL of autologous PRP for injection. Platelet concentration in the PRP was found to be $100–300 \times 10^9$/mL, which is four to five times greater than that of native peripheral blood. Under fluoroscopic guidance, a 21-gauge spinal needle was placed into the facet joint space. Contrast was then injected for confirmation. The targeted joint then received 0.5% lidocaine followed

by 0.5 mL of the PRP injectate. Follow-up visits took place at 1 week, 1 month, 2 months, and 3 months. At 1 week, patients reported significant decrease in LBP during flexion and at rest. At 1 month and 2 months, 15/19 patients reported "good" or "excellent" outcomes post-procedure. Of note, 9/19 of these patients reported good or excellent results immediately post-treatment, and 14/19 patients reported these results 1 week after treatment. Statistically significant differences were observed based on Roland-Morris Disability Questionnaire (RMQ), and a more than 10% improvement in lumbar functional capacity was observed based on ODI between pre-treatment and post-treatment. A clinically significant change from 6.68 to 2.63 on the VAS was observed. Prior to treatment, 17 patients (89.47%) were reported to be at the severe disability level or above; meanwhile, 2 patients (10.53%) reported moderate disability. Three months post-treatment, all the 19 patients (100%) were reported to be at the moderate disability level or below.

Aufiero et al. [18] performed a single-center observational case series with a set of five patients suffering from LBP hypothesizing that PRP may alleviate facet-mediated LBP. This case series consisted of patients lacking significant evidence of disc-mediated pathology visible on MRI who had failed conservative management including lumbar medial branch radiofrequency ablation (RFA) after receiving pain relief with medial branch block (MBB), physical therapy, trigger point injections, and analgesics. The average age of patients 54.6 years and follow-up evaluation took place at 6 and 12-month intervals. Autologous peripheral blood sample was collected from each patient for PRP preparation. PRP was obtained using double-spin centrifugation with the aim of obtaining a platelet count of greater than 1,500,000. Using fluoroscopic or ultrasound guidance, the PRP preparation was then injected into the facet joints, capsules, and supraspinous and interspinous ligaments. Thoracic spine injections also included the costovertebral joints, while lumbar spine injections also included the sacroiliac and iliolumbar ligaments. Patients were instructed to participate in relative immobilization for a minimum of 72 h post-procedure with bracing. Case 1: Patient received three PRP injections 1 month apart and reported 60% symptom improvement following second injection 100% improvement and d return to sport at 6 months; case 2: at least 30% symptom improvement following first injection, 60% improvement following the second series, and 1/10 VAS scale at 9 months; case 3: at least 40% symptom improvement following second injections, 2/10 VAS scale and improvement in functional status at 12 months; case 4: 70% symptom improvement and increased functional status following third injections; case 5: 65–70% symptom improvement and increased functional status at 6-month follow-up. Patient reported reduced fear and anxiety over inciting events, improved sleep, and decreased pain medication use.

Finally, in a combination study, Kirchner et al. [14] conducted a single-center observational study to assess the clinical outcome after one intradiscal, one intraarticular facet, and one transforaminal epidural injection of plasma rich in growth factors (PRGF) under fluoroscopic guidance. Eighty-six patients with a history of chronic LBP that lasted for greater than 3 months who failed conservative therapy consisting of pain management with oral nonsteroidal anti-inflammatory drugs (NSAIDs) and/or myorelaxant drugs were eligible to participate. Patients with failed back surgery syndrome were also considered to be eligible for participation in the trial. The median age for male participants was 55, and the median age for females was 58. Autologous peripheral blood samples were collected from each participant. The blood was then centrifuged and processed per protocol. Needle placement was performed using fluoroscopic guidance. The PRGF injectate was then introduced into disc, intraarticular facet, and peridural percutaneous infiltration. Four milliliters of activated PRGF was injected into the nucleus pulposus; peridural infiltration injection consisted of 2 mL of activated PRGF, and 0.5 mL of activated PRGF was injected into each of the affected facet joints. The primary outcome measure utilized was the VAS, and patients were evaluated at baseline, 1, 3, and 6-month intervals post-procedure. Pain scores demonstrated a statistically significant drop from 8.4 ± 1.1 before the treatment to 4 ± 2.6, 1.7 ± 2.3, and 0.8 ± 1.7 at 1, 3, and 6 months after the treatment, respectively, with respect to all the time evaluations ($p < 0.0001$) except for the pain reduction between the 3 and 6 months whose signification was lower ($p < 0.05$). The analysis of the VAS over time showed that at the end point of the study (6 months), 91% of patients showed an excellent score, 8.1% showed a moderate improvement, and 1.2% were in the inefficient score.

Discussion

LBP is a complex and common pathology that is a leading cause of disability in the USA [4]. LBP is generally thought to be mediated by two mechanisms: intervertebral disc-mediated pain or facet-mediated pain. Degeneration of the intervertebral disc (IVD) manifests as changes observed at both the gross and histological levels. Notable changes include a decrease in the presence of glycosaminoglycans, increase in matrix-degrading enzymes, altered distribution of structural matrix elements (i.e., collagen type I, III, VI, and X, elastin, fibronectin, and amyloid), and there is increased apoptosis or cell death [3••]. This alteration of the healthy microenvironment of the IVD is largely a function of upregulation of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α and downregulation of

regenerative factors such as insulin-like growth factor (IGF), transforming growth factor-β (TGF-β), and bone morphogenic proteins (BMPs) [19]. These same pro-inflammatory cytokines have also been implicated in the pathogenesis of facet-mediated LBP [20]. Increased attention to this pro-inflammatory signaling cascade has contributed to the popularity of regenerative approaches to ameliorate the symptoms, and potentially the pathology, associated with LBP. Growth factors aimed at potentiating regeneration derived from autologous sources such as MSC, PRP, PL, and SVF have been investigated and evaluated in this systematic review.

The seven articles analyzed in this systematic review present promising data regarding the use of these autologous biologic treatments, but many of these investigations have several limitations in common. Small sample sizes detract from the power of the data presented in each of these articles, only one of which had a large sample size ($n = 470$), performed by Centeno et al. [13] In addition, there is extensive debate regarding the NRS and VAS consisting of only an ordinal, rather than the more robust ratio or interval, scale measurement when it comes to a variety of outcomes, even in the context of rehabilitation [21]. This may, however, be a limitation in any trial attempting to alleviate pain due to the subjectivity inherent to pain reporting by patients and the fact that no completely objective assessment of pain is available.

Several of these trials were performed as open-label trials, which lack randomization, a control group, and blinding of both the study participant and administering physician. The trial conducted by Kirchner et al. [14] performed injections of growth factors into disc, intraarticular facet, and peridural percutaneous infiltration. This model makes it difficult for discerning practitioners to determine which injection may have been responsible for symptom relief observed in their investigation. Similarly, Comella et al. [10] prepared SVF and PRP for injection, which renders the biologic responsible for positive results unidentifiable.

Wu et al. [15] found that patients experienced pain relief immediately and 1-week post-procedure, which is insufficient time for any growth factors to regenerate tissue and may be a function of placebo or local anesthetic. This evidence demonstrates a need to perform a comparison between biologic injectate and saline or placebo and additional exploration of the length of time it takes for the healing factors found in these biologics to take effect. The incorporation of biomarkers into the trial performed by Cuellar et al., while novel, may prove to be too expensive to integrate into clinical practice. Centeno et al. [13] utilized hydrocortisone in their injection protocol. While the quantity may have been negligible, this small amount may have altered the contents of their injectate and, consequently, their data. Additionally, there is insufficient evidence to determine if one or several injections are required to provide demonstrable improvement. There are still many questions regarding regenerative medicine that remain unanswered. One of these questions is whether to use leukocyte-rich versus leukocyte-poor concentrations of PRP injectate and which populations would receive the most benefit from these procedures.

It is important to note the lack of significant adverse events resulting from these procedures. Only two of the seven trials reviewed reported adverse events. Four patients reported increased pain symptoms immediately post-procedure, three had symptoms consistent with dural puncture, and only one required intervention with an autologous blood patch. This represents a lack of adverse effects in 97.42% of the patients who participated in the clinical trials discussed in this review. Tuaki-Wosornu et al. [16] raise the question regarding the necessity of pre-procedural antibiotics in their randomized control trial evaluating the efficacy of intradiscal PRP. This was the only study that utilized antibiotics to prevent infection, which makes evaluators question the use of antibiotics to prevent infections, including discitis, when performing regenerative intradiscal procedures. This necessitates further investigation to determine if antibiotics may have a role in enhancing the safety of these types of procedures.

The present investigation has several limitations. The small, geographically limited inclusion criteria decrease the power of our analysis. Requiring very recently published material may, too, have decreased the power of our conclusions. The low levels of evidence present in the aggregate of these articles prevent the researchers from establishing concrete conclusions regarding the efficacy of these regenerative procedures. Moreover, inclusion criteria discussed by Wu et al. [15] included pain with flexion, a symptom typically not associated with facet-mediated back pain. This is indicative of the need of more rigid inclusion criteria to cull a more precise sample—and the flaws inherent to the investigations presented here.

Despite these limitations, the positive results observed in these clinical trials warrant attention. Regenerative procedures, such as those outlined in this systematic review, will only increase in popularity, particularly within the context of low back pain. This promising data represents an opportunity to affect significant change and improve patient quality of life for sufferers of low back pain and affords this population an alternative to the current standard of care that includes corticosteroid injections or surgical intervention. It is the responsibility of astute clinicians to ensure the safety of these regenerative procedures. Therefore, additional large-scale, randomized control trials should be performed to further determine the safety, efficacy, and long-term effects of regenerative procedures aimed at relieving low back pain. Long-term efficacy is of importance given the unknown long-term effects and unknown duration of efficacy. This research should focus on clinical, rather than statistical, significance to better determine benefit conferred to patients. It would also be appropriate to perform cost analysis and standardization to determine

expense to patients because at this time, regenerative procedures of this nature are not covered by insurance plans, which will prompt a moral quandary: are individuals with financial resources in the USA the only population who can benefit from regenerative medicine?

Compliance with Ethical Standards

Conflict of Interest Ali Valimahomed, Paul Ryan Haffey, Richard D. Urman, Alan D. Kaye, and R. Jason Yong declare no conflict of interest. Alan Kaye is on the speaker bureau for Merck and Depomed, Inc. Richard D. Urman has received honoraria from Medtronic, Merck and 3M.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Theis KA, Roblin DW, Helmick CG, Luo R. Prevalence and causes of work disability among working-age U.S. adults, 2011–2013, NHIS. Disabil Health J. 2018;11(1):108–15.
2.•• Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. J Bone Joint Surg Am. 2006;88(Suppl 2):21–4 **Excellent review of socioeconomic factors and consequences of low-back pain**.
3.•• Roberts S, Evans H, Trivedi J, Menage J. Histology and pathology of the human intervertebral disc. J Bone Joint Surg Am. 2006;88(Suppl 2):10–4. https://doi.org/10.2106/JBJS.F.00019 **Excellent review of histology and pathology of the human disc**.
4. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. Lancet. 2017;389(10070):736–47.
5.•• Hoy D, Brooks P, Blyth F, Buchbinder R. The epidemiology of low back pain. Best Pract Res Clin Rheumatol. 2010;24(6):769–81 **Excellent review of epidemiology of low-back pain**.
6.•• Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. Nat Rev Rheumatol. 2013;9(4):216–24 **Excellent review of pathophysiology of osteoarthritis as it pertains to the facet joints**.
7. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost [Internet]. 2003 [cited 2018 May 19]; **Available from:** http://www.schattauer.de/index.php?id=1214&doi=10.1160/TH03-07-0440&no_cache=1
8. Charo RA, Sipp D. Rejuvenating regenerative medicine regulation. N Engl J Med. 2018;378(6):504–5.
9. Sobajima S, Vadala G, Shimer A, Kim JS, Gilbertson LG, Kang JD. Feasibility of a stem cell therapy for intervertebral disc degeneration. Spine J. 2008;8(6):888–96.
10. Comella K, Silbert R, Parlo M. Effects of the intradiscal implantation of stromal vascular fraction plus platelet rich plasma in patients with degenerative disc disease. J Transl Med [Internet]. 2017 [cited 2018 May 2];15(1). Available from: http://translational-medicine.biomedcentral.com/articles/10.1186/s12967-016-1109-0
11. Doucet C, Ernou I, Zhang Y, Llense J-R, Begot L, Holy X, et al. Platelet lysates promote mesenchymal stem cell expansion: a safety substitute for animal serum in cell-based therapy applications. J Cell Physiol. 2005;205(2):228–36.
12. Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months: autologous BMC injection reduces discogenic pain. Stem Cells. 2015;33(1):146–56.
13. Centeno C, Markle J, Dodson E, Stemper I, Hyzy M, Williams C, et al. The use of lumbar epidural injection of platelet lysate for treatment of radicular pain. J Exp Orthop [Internet]. 2017 Dec [cited 2018 May 13];4(1). **Available from:** https://jeo-esska.springeropen.com/articles/10.1186/s40634-017-0113-5
14. Kirchner F, Anitua E. Intradiscal and intra articular facet infiltrations with plasma rich in growth factors reduce pain in patients with chronic low back pain. J Craniovertebral Junction Spine. 2016;7(4):251.
15. Wu J, Du Z, Lv Y, Zhang J, Xiong W, Wang R, et al. A new technique for the treatment of lumbar facet joint syndrome using intra-articular injection with autologous platelet rich plasma. Pain Physician. 10.
16. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Harrison JR, Gribbin CK, LaSalle EE, et al. Lumbar intradiskal platelet-rich plasma (PRP) injections: a prospective, double-blind randomized controlled study. PM&R. 2016;8(1):1–10.
17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), chronic pain grade scale (CPGS), Short Form-36 Bodily Pain Scale (SF). Arthritis Care Res. 2011;63(S11):S240–52.
18. Aufiero D, Vincent H. Regenerative Injection Treatment in the Spine: Review and Case Series with Platelet Rich Plasma. J Stem Cells Res, Rev & Rep - Volume 2 Issue 1.- 2015
19. Wiet MG, Piscioneri A, Khan SN, Ballinger MN, Hoyland JA, Purmessur D. Mast cell-intervertebral disc cell interactions regulate inflammation, catabolism and angiogenesis in discogenic back pain. Sci Rep [Internet]. 2017 [cited 2018 Jun 4];7(1). **Available from:** http://www.nature.com/articles/s41598-017-12666-z
20. Igarashi A, Kikuchi S, Konno S, Olmarker K. Inflammatory cytokines released from the facet joint tissue in degenerative lumbar spinal disorders. Spine. 2004;29(19):2091–5.
21. Price D, Staud R, Robinson M. How should we use the visual analogue scale (VAS) in rehabilitation outcomes? II: visual analogue scales as ratio scales: an alternative to the view of Kersten et al. J Rehabil Med. 2012;44(9):800–1.
22. Cuellar JM. Intradiscal Injection of an Autologous Alpha-2-Macroglobulin (A2M) Concentrate Alleviates Back Pain in FAC-Positive Patients. Orthop Rheumatol Open Access J [Internet]. 2017 Jan 3 [cited 2018 May 2];4(2). Available from: https://juniperpublishers.com/oroaj/OROAJ.MS.ID.555634.php