



Regenerative Medicine: Pharmacological Considerations and Clinical Role in Pain Management

Alan D. Kaye¹ · Amber N. Edinoff² · Yale E. Rosen³ · Megan A. Boudreaux³ · Aaron J. Kaye⁴ · Meeta Sheth¹ · Elyse M. Cornett^{1,9} · Vanessa Moll^{5,6} · Claudia Friedrich⁵ · Johan Sibrecht Verhagen⁵ · Berthold Moser^{7,8} · Annu Navani^{8,9,10}

Accepted: 27 June 2022 / Published online: 8 September 2022

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Abstract

Purpose of Review Low back pain affects at least 80% of individuals at some point in their lifetime and is the fifth most common reason for physician visits in the USA. Treatment of an acute episode of LBP generally includes rest, activity modification, physical therapy, NSAIDs, and patient education.

Recent Findings A small percentage of patients will develop chronic pain lasting > 6 months duration. Platelet-rich plasma (PRP) is one of the main pillars of regenerative medicine, as its release of bioactive proteins supports the aim of RM of restoring the anatomical function in degenerative conditions. Mesenchymal stem cells (MSCs) are multipotent stem cells, multipotent progenitor cells, or marrow stromal cells found in various body tissues, including bone marrow, lung, and adipose tissue. Evidence from well-designed case–control or cohort studies for the use of PRP and MSCs in lumbar facet joint, lumbar epidural, and sacroiliac joint injections is currently described as level IV evidence. PRP and MSCs are used autogenously to help facilitate the healing process, and their injection has been studied in the long-term management of discogenic low back pain. PRP has been compared to steroid injections in the sacroiliac joint for chronic low back pain, with favorable results. MSCs have also been shown to be useful in intervertebral disc regeneration and treatment of chronic low back pain associated with degenerative disc disease.

Summary Currently, the price for these treatments is extremely high, and thus the standard of care continues to be steroid injections and other treatments. This could change, however, with more robust data and research on the safety and long-term efficacy of biologics compared to other interventional management.

Keywords Platelet-rich plasma · Mesenchymal stem cells · Back pain · Regenerative medicine · Biologics

This article is part of the Topical Collection on *Regenerative Pain Medicine/Interventional Pain Medicine*

Highlights

- At least 80% of people will experience low back pain during their lifetime, and it is the fifth most common reason for medical visits in the USA. A small proportion of patients will experience chronic pain that lasts more than 6 months.
- Platelet-rich plasma (PRP) is a critical component of regenerative medicine, as its release of bioactive proteins contributes to the goal of RM, which is to restore anatomical function in degenerative conditions. Mesenchymal stem cells (MSCs) are multipotent stem cells, multipotent progenitor cells, or marrow stromal cells that are present in a variety of body tissues, including bone marrow, the lung, and adipose tissue.
- Evidence from well-designed case-control or cohort studies for the use of PRP and MSCs in lumbar facet joint, lumbar epidural,

and sacroiliac joint injections is currently described as level IV evidence.

- Autologous PRP and MSCs are used to aid in the healing process, and their injection has been studied in the long-term treatment of discogenic low back pain.
- At the moment, the cost of these procedures is still prohibitively high, and as a result, steroid injections and other treatments continue to be the standard of care. This can improve, however, as rigorous evidence and analysis on the safety and long-term effectiveness of biologics are accumulated in comparison to other forms of interventional management.

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Introduction

Back pain is an extremely common problem that is experienced by people of all ages [1, 2]. Specifically, low back pain (LBP) affects at least 80% of individuals at some point in their lifetime and is the fifth most common reason for physician visits in the USA. LBP is a leading cause of activity limitation and work limitation throughout much of the world, second only to upper respiratory conditions [3]. LBP is also now the number one cause of disability in most countries [4]. Analysis of USA spending on personal health care, public health, and increases of healthcare costs from 1996 to 2013 showed estimated spending of 87.6 billion in low back and neck pain, the third-highest healthcare cost among different disease categories [5, 6, 7]. In addition, LBP and neck pain had the second-largest increase in spending associated with it [6]. This is likely to increase with the global aging population [1]. The vast majority of people will be diagnosed with “non-specific” LBP [8]. Once specific causes of LBP (malignancy, fracture, infection) have been ruled out, it is important to differentiate mechanical and inflammatory LBP from one another.

Mechanical LBP is an injury or derangement to the anatomic structure of the low back. When not due to an emergent cause, mechanical LBP is associated with a good prognosis, and management is conservative and includes patient education focused on massage, exercise, and behavioral approaches to minimize injury [9, 10]. Acupuncture and herbal supplements can be effective as well [9, 11]. Inflammatory back pain results from a systemic inflammatory condition, often axial spondyloarthritis. Inflammatory back pain can be distinguished from mechanical back pain due to a younger age of onset, improvement with exercise, pain at night, insidious onset, and no improvement at rest. These patients should be treated with structured exercise, non-steroidal anti-inflammatories (NSAIDs) and should be referred to rheumatology [9]. Regardless of mechanical or inflammatory etiology, it has been seen that most patients with acute or subacute LBP improve over time regardless of treatment, so management should initially be conservative, nonpharmacologic, and non-invasive [11].

Treatment of an acute episode of LBP generally includes rest, activity modification, physical therapy, NSAIDs, and patient education. A small percentage of patients will develop chronic pain lasting > 6 months duration. Clinicians have a very limited ability to detect the exact source of the pathology in this case. This makes cure unlikely, and care should be supportive, with a goal to improve pain and function [3]. For patients with chronic LBP who have an inadequate response to conservative and pharmacological treatment, a number of techniques have been established. These include complex spinal fusions, image-guided interventional techniques, and regenerative

medicine therapies such as injection of platelet-rich plasma (PRP) and mesenchymal stem cells (MSC) [5, 12–14]. The success of PRP and MSC in athletes has brought these into the spotlight. This paper seeks to provide further investigation and comparison to determine the efficacy and safety of biologics in the treatment of LBP.

Current Treatment of Chronic Back Pain

Musculoskeletal (MSK) pain is defined as acute or chronic pain that affects bones, muscles, ligaments, tendons, and even nerves. The most prevalent forms of musculoskeletal pain are chronic low back pain (LBP), neck pain, and the pain associated with osteoarthritis and rheumatoid arthritis, which is found in the joints. The International Association for the Study of Pain (IASP) defines chronic pain as “pain that exists beyond an expected time frame for healing” [15], commonly pain beyond 12 weeks [16]. A total of 10–40% of patients with acute or subacute low back pain continue to have symptoms beyond 6 weeks [16]. A multidisciplinary, logical approach to chronic LBP treatment is most effective, with medical, psychological, physical, and interventional approaches included [17].

The College of American Physicians’ clinical practice guidelines gives the following recommendations for the non-invasive treatment of chronic low back pain [11]:

1. Clinicians and patients should emphasize nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction, tai chi, yoga, motor control exercise, progressive relaxation electromyography feedback, low-level laser therapy, operant therapy, or cognitive behavioral therapy.
2. Patients who do not respond adequately to nonpharmacological therapy can be treated with medications. Nonsteroidal anti-inflammatory drugs are a first-line and medications such as tramadol or duloxetine second-line therapy. Opioids should only be considered if patients have failed both therapies and the potential benefits outweigh the risks of opioid treatment.

A systematic review of randomized controlled trials, which assessed conservative treatment options for low back pain, found strong evidence for the use of muscle relaxants, manipulation, education (“back school”), and exercise therapy [18]. If conservative treatments are unsuccessful, invasive methods, such as steroid injections, nerve blocks, cryoablation, radiofrequency ablation (RFA), or surgery, can be attempted. Most studies use RFA to treat lumbar facet and sacroiliac joint pain and suggest significantly reduced pain in the short-term follow-up. RFA treatment for discogenic pain shows mixed results [19]. A small number of patients suffering from low

back pain require surgery. For the small minority of low back pain patients with severe or progressive motor weakness or signs and symptoms of cauda equina syndrome, urgent evaluation by a spinal surgeon is indicated. A systematic review evaluating total disk replacement, fusion, cognitive behavioral therapy, and physical therapy could not conclude which treatment was best for chronic LBP [20].

The management of spinal pain requires the appropriate diagnoses and effective evidence-based treatments [21•, 22, 23]. Recently, regenerative medicine has entered the field of MSK disorders, including LBP [5•]. Platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are the current mainstays of regenerative medicine treatment.

What Is the Use of Platelet-Rich Plasma (PRP) in Regenerative Medicine?

Platelet-rich plasma (PRP) is one of the main pillars of regenerative medicine (RM), as its release of bioactive proteins supports the aim of RM of restoring the anatomical function in degenerative conditions by “replacing, engineering or regenerating human cells, tissues or organs” [11, 15–17]. Supporting evidence for the effectiveness of PRP treatment for several forms of lower back pain (LBP) is still scarce due to its relative newness. To date, only smaller studies lacking standardized PRP protocols exist [11, 15–20, 21•]. However, PRP seems to be a promising therapy option to treat forms of LBP.

How Do You Harvest?

There are different techniques available. One is through an aseptic venipuncture, where 30–60 mL of autologous whole blood is drawn and gets centrifuged for 15 min at 3200 rpm [11, 17, 22]. The resulting blood is divided into platelet-poor plasma, platelet-rich plasma (PRP), RBC, and WBC. To resuspend the PRP, it gets shaken for 30 s; others centrifuge the PRP again to increase its concentration even further [17, 23]. After these processes, the PRP gets withdrawn, resulting in 3–6 cc of PRP [17].

Ideal Platelet Concentrations

The exact platelet preparation and PRP concentration are not standardized and are still under investigation [11]. The PRP concentration recommendations range from 2.5 to 6 times greater than the “normal” peripheral plasma concentration, with absolute numbers varying between 200 to 1200×10^9 platelets/L [5•, 21•, 24–26, 27•, 28–31]. A fixed concentration (classification system) should generally be agreed upon to improve the comparisons between past and upcoming research results.

What Are MSCs?

Mesenchymal stem cells (MSCs) have a unique potential for cell-based therapies due to their minor immunogenicity and significant effects on tissue regeneration [32, 33]. MSCs are multipotent stem cells, multipotent progenitor cells, or marrow stromal cells found in various body tissues, including bone marrow, lung, and adipose tissue [34].

The Versatility of Mesenchymal Stem Cells and Their Use for Regenerative Medicine

They are defined by their ability of cell surface proteins to adhere and by their ability to differentiate into osteogenic, chondrogenic, and adipogenic lineages [35, 36]. A recent study has shown promising results for applying MSC in tumor-specific immune modulation and possibly a cancer vaccination [37]. Recently, MSC found in umbilical cord tissue, placental tissue, and menstrual blood, for example, may have regenerative potential in COVID-19 as the use of MSC alleviated ARDS symptoms like dyspnea and significantly lowered mortality [34].

When induced with signaling growth factors and in respective microenvironments [38], MSC can acquire various other properties such as cardiomyocytic or hepatocytic properties [39–41]. They can be used as autologous or allogeneic grafts [42]. Both autologous and allogeneic MSC display immunomodulatory behavior and have low immunogenic potential, thereby having a favorable profile for cell-based therapies [43, 44].

How Are MSC Harvested and Injected for Therapy?

MSC can easily be harvested from bone marrow and adipose tissue then expanded in cell cultures in vitro. To facilitate disc regeneration, different amounts of MSC have been recommended [45]; the amounts used at present range from 25×10^6 /L of allogeneic bone marrow-derived MSC suspended in 2 mL injection volume and with an expansion time of 27 days \pm 2 days [44] to $15.1\text{--}51.6 \times 10^6$ /L of autologous MSC in 0.25–1 mL and no expansion time [46] to autologous bone marrow concentrate with 2713 CFU-F/mL in 6 mL (2–3 mL per disc) [47]. Alternatively, $10 \pm 5 \times 10^6$ autologous bone marrow-derived MSC can be used and cultured for 24 \pm 4 days [48]. Culture expansion might reduce the heterogeneous MSC population over time, altering or reducing paracrine activities and function [40]. MSCs are then collected from the tissue culture flasks, trypsinized, centrifuged, pelleted, and resuspended in liquid ice-cold collagen fibronectin gel. The collagen fibronectin gel forms a soft gel at body temperature

[49]. The MSC mixture can be sterilely injected into the target tissue [50]. The expanded and cultured MSCs are currently not allowed for clinical use in the USA.

How Are Autologous and Allogeneic Stem Cell Therapies Used in Back Pain?

Degenerative intervertebral disc disease is thought to be caused by a deficit of nutrients, oxygen, acidic pH, making the disk prone to injury, which causes the weakening and skewing of the extracellular matrix. In addition, there is a shift of production from collagen type II to I and a decreased aggrecan synthesis, which further shrinks the disc and reduces the proteoglycan buffer serving as mechanical support between vertebrae. The avascular intervertebral discs are known to have limited self-regenerating capacity, diminished nutrient and oxygen supply and low cellularity, and abundant hydrated extracellular matrix.

At present, no clinical therapy exists that fully reverses disc degeneration. However, MSC can alleviate discogenic lower back pain (LBP) by modulating primary nociceptive disc pain, reversing or slowing catabolism, and regenerating disc tissue [43]. MSCs have been shown to reduce inflammation in degenerated disc tissue mediated by cytokines such as IL-1, IL-6, IL-17, and TNF α , and they secrete growth factors enhancing tissue regeneration [51, 52]. MSC can alleviate the effects of hypoxia, malnutrition, and acidosis. Aging processes may be slowed, and mechanical properties improved [43, 53, 54]. MSCs secrete trophic factors that improve tissue homeostasis, reduce inflammation, modulate the microenvironment, and even acquire properties of the nucleus pulposus, which synthesizes ECM components [55].

Patients treated with bone-marrow-derived MSC by intradiscal injection displayed a rapid relief of back pain in 40% of the patients with an improvement in bone density in the MSC-treated intervention group at 1-year follow-up [44].

Additives to Enhance MSC Treatment

The survival of injected cells currently is a limiting factor for lasting results. Several weeks post-injection, MSCs are remodeled or have become apoptotic. The concomitant use of hyaluronic acid appears to hydrate the disc and work synergistically with osteogenically induced MSC [51]. The combination of MSC with growth factors like bone morphogenetic protein (BMP)-2 (induces osteogenesis) and TGF- β (decreases inflammation, mediates chondrogenic differentiation of MSC), LIM mineralization protein-1 (LMP-1; a key regulator of osteoblast differentiation) [56], chondroitinase ABC (from proteus vulgaris; increases axonal sprouting and regeneration in spinal cord injury)

[57], tissue inhibitor of metalloproteinases (TIMP; impact MSC function, osteogenic differentiation, matrix remodeling in bone regeneration) [58], and SOX9 (modulates cell survival and promotes osteogenic differentiation) [59] has shown promise in reversing intervertebral disc disease and therefore effectively reducing lower back pain [60, 61]. In a 6-year study utilizing MSC in degenerative disc disease, the disease process was reversed. Transplanted MSC produced ECM, with the most prevalent being proteoglycan aggrecan, which led to rebuilding the previous height of intervertebral discs [51].

The Immunomodulatory Effects of MSC and Current Clinical Trials

Further studies are needed to investigate the immunomodulatory effects, the paracrine and autocrine activities, and how to potentially guide them into non-harmful differentiation and long-term effects, in particular the potential for tumorigenesis, long-term and immunomodulatory effects [50, 62]. MSCs have a strong case for future translational research and clinical applications. So far, more than 188 clinical phase 1 and 2 trials have been completed, and a dozen clinical phase 3 trials registered at www.clinicaltrials.gov, totaling a patient enrollment of about 50,000 patients [40, 63]. One hundred six studies are currently registered on clinicaltrials.gov assessing the use of MSC in low back pain. Standardization of protocols and automated production methods and collaboration with the industry is warranted to manufacture regenerative therapies such as MSC in sufficient amounts [33].

Establishing Safe Protocols for the Use of Biologics in Humans

ASIPP recently established guidelines for the effective use and management of biologics in lumbar spine disease [64]. Evidence from well-designed case-control or cohort studies for the use of platelet-rich plasma (PRP) and MSCs in lumbar facet joint, lumbar epidural, and sacroiliac joint injections is currently described as level IV evidence [64].

To improve the therapeutic effect of MSCs while reducing potential side effects, biosafety testing protocols should be implemented. An example of a protocol is found in the Canadian regulations for cellular and gene therapy products [65]. Autologous MSCs are considered safe for transplantation [50, 62]. Both autologous and allogeneic MSC are effective with few side effects and are considered relatively safe [66]. Generally, a multimodal therapeutic approach to back pain, including physical exercise, behavioral and medical therapy, is supported.

Clinical Studies on the Use of PRP in the Treatment of Chronic Back Pain

Evidence supporting the implementation of regenerative medicine as a viable treatment modality has been demonstrated by several randomized control trials (RCTs). One study conducted by Singla and colleagues in 2016, comprised of a 40-patient cohort, compared the use of steroids versus platelet-rich plasma (PRP) for the treatment of chronic low back pain secondary to some form of sacroiliac joint pathology. Overall, the study concluded that PRP demonstrated greater efficacy in the treatment of lower back pain when compared with traditional steroid injections. In the study, the patients were subdivided into two groups. Group S, the steroid group, received an ultra-sound guided sacroiliac joint injection of 1.5 mL methylprednisolone plus 1.5 mL of 2% lidocaine with 0.5 mL saline. Group P, the PRP group, received 3 mL of leukocyte-free PRP with 0.5 mL of calcium chloride. Visual analog scale (VAS) scores were used to quantitatively assess the pain intensity experienced by the patients. Group P reported significantly lower VAS scores at 6 weeks and 3 months. Additionally, Modified Oswestry Disability Questionnaire (MODQ) and Short Form (SF-12) Health Survey Scores were evaluated. Group P demonstrated both improved MODQ and SF-12 scores throughout the entire 3-month study period, while group S only demonstrated improved scores in the first 4 weeks [67].

In addition to sacroiliac joint pathologies, several studies have been conducted to measure the efficacy of PRP in intradiscal lumbar injections. In one RCT conducted by Tuakli-Wosornu and associates, a total of 47 participants with a history of chronic lower back pain were allocated to the treatment group (29 of the participants) or the control group (18 of the participants). Patients in the treatment group received 3–4 mL of autologous PRP, while patients in the control group received a contrast agent. The outcomes of pain and functional improvement were quantified using the Functional Rating Index (FRI), the Numeric Rating Scale (NRS), a modified North American Spine Society (NASS) Outcome Questionnaire, and the 36-item Short Form (SF-36) Health Survey. Overall, the study concluded that patients in the treatment group had significant improvements in their FRI, NRS, and NASS scores in the first 8 weeks of the trial. Of note, no adverse outcomes secondary to the intradiscal injections, including disc space infection or disc herniation, were reported in the 1-year follow-up period in which the trial was conducted [68]. One prospective trial on the use of PRP intradiscal lumbar injections demonstrated that 47% of patients in a 22-participant cohort demonstrated at least a 50% improvement in their pain, as measured via the VAS scoring system, at their 6-month follow-up appointment. However, only 14% of patients in this cohort reported at least a 50% pain improvement at their 1-month follow-up

appointment. The authors attributed this largely to the mechanism of PRP as a restorative treatment that requires time to be effective [69].

Epidural PRP injections are also being investigated in the treatment of spinal pain. A RCT conducted by Ruiz-Lopez and Tsai selected 25 patients out of a 50-patient cohort to receive 16.5 mL of leukocyte-rich platelet-rich plasma (LR-PRP) plus 3.5 mL of non-ionic iohexol contrast medium, which was injected into the epidural space between S3 and S4 under fluoroscopy. The remainder of participants in the control group was injected with triamcinolone acetonide 60 mg. Similar to prior studies investigating the analgesic effects of PRP, patients in the control group had lower VAS scores at the 1-month follow-up appointment. However, at the 3- and 6-month follow-up visits, patients in the LR-PRP group had lower VAS scores, demonstrating that PRP is most effective as a long-term therapeutic analgesic [70].

A preliminary clinical trial conducted in 2017 by Akeda and colleagues analyzed the safety and efficacy of utilizing autologous PRP in the treatment of discogenic back pain. The study was carried out over a 10-month period, and 71% of patients reported a 50% pain reduction, as quantified by the VAS scoring system, with 2 out of the 14 patients reporting a return of their lower back pain by the conclusion of the study. Additionally, 79% of the patients demonstrated a 50% reduction in their Roland-Disability Questionnaire (RDQ) scores throughout the study period. However, the RDQ scores increased in the same two patients whose lower back pain also returned. In terms of safety, the only adverse events reported were transient leg numbness reported by two different patients at 1 and 6 months post-treatment. Both of these patients reported complete resolution of their symptoms within 1 week of onset [71]. Table 1 is a summary of the clinical studies investigating PRP in the treatment of lower back pain.

Clinical Studies on the Use of Mesenchymal Stem Cells in the Treatment of Chronic Back Pain

In addition to PRP, the use of autologous stem cells in the treatment of chronic back pain is currently undergoing rigorous assessment. Of note, Kumar and colleagues conducted a single arm phase-1 clinical trial in 2017, in which 10 patients with chronic lower back pain were enrolled in a 12-month trial and received a one-time intradiscal injection that was comprised of a combination of hyaluronic acid (HA) and autologous adipose tissue-derived mesenchymal stem cells (AT-MSCs) with dosages of 2×10^7 cells/disc ($N=5$) or 4×10^7 cells/disc ($N=5$). The primary outcome of the study was an analysis of the safety and tolerability AT-MSC transplants, and no adverse events were observed within the 1-year follow-up period. Additionally, the VAS, ODI, and SF-36 scores improved in both groups, with no statistically significant difference noted between the

Table 1 Summary of clinical studies on PRP in the treatment of lower back pain

Study	Population	Treatment	Outcome measures	Results	Conclusion
Singla et al. (2016) [67] N=40 Follow-up = 2 weeks, 4 weeks, 5 weeks, 3 months Prospective randomized, open blinded endpoint (PROBE) study	40 patients, both male, and female, 18–65 years old with chronic low back pain with VAS score > 3 for more than 3 months	3 mL of leukocyte-free PRP plus 0.5 mL of calcium chloride administered via ultrasound-guided sacroiliac joint injection	VAS, MODQ, SF-12	<ul style="list-style-type: none"> Patients treated with PRP showed significantly lower VAS scores at 6 weeks and 3 months when compared with patients receiving only traditional steroid injections MODQ and SF-12 scores in patients receiving PRP injections demonstrated improvement of symptoms and disability in the three months that the patients were followed while group S (MODQ and SF-12 scores only showed improvement for the first 4 weeks) 	Intra-articular PRP injections are an effective treatment modality in the management of chronic lower back pain
Tuakli-Wosomu et al. (2016) [68] N=47 Follow up = 1 week, 4 weeks, 8 weeks, 6 months, and 1 year Prospective, double-blind, randomized controlled study	47 patients with history of chronic lower back pain for more than 6 months who had previously failed conservative treatment	3–4 mL of autologous PRP intradiscal lumbar injections	FRI, NRS, SF-36, modified NASS Outcome Questionnaire	<ul style="list-style-type: none"> FRI, NRS, SF-36, and NASS scores were all significantly improved in the first 8 weeks of the trial when compared to the control group No adverse events secondary to the treatment were reported in the 1-year follow-up period 	Intradiscal lumbar injections are safe and efficacious in the management of adult lower back pain
Levi et al. (2016) [69] N=22 Follow up = 1 month, 2 months, and 6 months Prospective trial	22 patients over the age of 18 who had clinical or radiographic features suggestive of discogenic pain source	1.5 mL of autologous PRP intradiscal lumbar injections	VAS, ODI	<ul style="list-style-type: none"> Patients with a 50% improvement in VAS and a 30% improvement in ODI were considered a success At 6-month follow-up, 47% of patients had a 50% improvement in VAS and a 30% improvement in ODI 	Intradiscal lumbar injections have demonstrable efficacy in the management of adult lower back pain within the first 6 months of having the treatment. However, RCTs are needed to further evaluate
Ruiz-Lopez and Tsai (2020) [70] N=50 Follow-up = 1 month, 3 months and 6 months Prospective randomized controlled double blinded study	50 patients with degenerative spinal pain; patients with lumbar pain should have had it lasted for at least 3 months	16.5 mL of leukocyte-rich PRP and 3.5 mL of non-ionic iohexol contrast medium injected into the epidural space between S3 and S4 under fluoroscopic guidance	VAS, SF-36	<ul style="list-style-type: none"> Patients who received LR-PRP (treatment group) and triamcinolone acetamide (control group) both had improved VAS scores in the 6-month follow-up periods At the 1-month follow-up period, the corticosteroid group had significantly lower VAS scores while at the 3- and 6-month follow-up appointments, patients receiving the LR-PRP injections had lower VAS scores 71% of patients reported a 50% pain reduction as quantified by the VAS scoring system 79% of the patients demonstrated a 50% reduction in their Roland-Disability Questionnaire (RDQ) scores throughout the study period 	Both corticosteroid and LR-PRP treatments can result in significant pain reduction, but LR-PRP may provide longer-lasting results
Akeda et al. (2017) [71] N=14 Follow-up = average was 10 months Preliminary clinical trial	14 patients reporting a history of chronic low back pain for three or more months, one or more lumbar discs with radiologic evidence of degeneration, and at least one symptomatic disc	2 mL of PRP released injected under fluoroscopy	VAS, RDQ	<ul style="list-style-type: none"> PRP is a safe and effective treatment for the management of chronic lower back pain with the only adverse events reported in the study period being transient leg numbness that resolved with 1 week of onset of symptoms 	

high- and low-dose groups. Six out of 10 patients achieved final treatment success, which was defined as a reduction of greater than or equal to 50% of their VAS and ODI scores when compared to pretreatment scores. Of these 6 patients, 3 were shown to have increased water content on MRI at the 1-year follow-up visit [72].

A pilot study conducted by Orozco and associates also demonstrated the clinical efficacy of mesenchymal stem cell transplants. In this trial, 10 patients were injected with autologous mesenchymal bone marrow stem cells and assessed over the 1-year study period via MRI scans, ODI scores, and VAS scores. Overall, water content was shown to be elevated 12 months post-treatment on MRI, and patients demonstrated significant improvements in pain and disability, with the treatment efficacy approaching 71%. The study found that 9 out of the 10 patients in the trial had consistent improvement in pain and disability, with only 1 patient having no demonstrable benefit post-treatment. Additionally, patients achieved 85% of their maximal improvement within the first 3 months post-treatment [48].

In addition to autologous treatment, allogeneic stem cell transplants are being thoroughly investigated. The appeal of allogeneic stem cells is that they could be derived from a source pool of healthy donors and distributed among patients. However, the risk of allogeneic stem cells is, of course, host immune rejection of the cells derived from a secondary source. One RCT conducted by Noriega and associates found that patients injected with allogeneic bone-marrow-derived stem cells demonstrated reduced lumbar pain and disability 3 months post-transplant, and these results were maintained throughout the entire 1-year study period. Consistent with other regenerative medicine studies, this RCT validated the ability of regenerative therapeutics to chronically, rather than acutely, manage symptoms. While patients in the control group, who received an injection of 2 mL of 1% mepivacaine, demonstrated an overall decrease in their VAS scores in the first 8 days post-treatment, patients in this group generally exhibited no further improvement of symptoms over the 1-year follow-up period. Comparatively, patients in the MSC treatment group only reached about 30% of the maximum improvement in their pain and disability within the first 8 days. Peak symptom improvement was only nearly complete at the 3-month follow-up appointment [44].

Most recently, in 2021, Amirdelfan and associates published their findings of a 36-month prospective randomized, placebo-controlled study on the use of allogeneic mesenchymal stem cells in the treatment of lower back pain. One hundred patients were randomly divided into one of four groups in a 3:3:2:2 ratio with patients receiving: (1) 6 million mesenchymal precursor cells (MPCs) with hyaluronic acid (HA), (2) 18 million MPCs with HA, (3) HA vehicle (control), or (4) sterile saline (placebo). All of the cells were sourced from a single donor, and the cells were injected directly into the intervertebral discs of the participants. After receiving the treatments, patients were

evaluated at 1-, 3-, 6-, 12-, 24-, and 36-month intervals. At these appointments, patients were subjected to a thorough, objective assessment comprised of physical exams, imaging, and labs, including HLA classes I and II donor-specific antibody assays. Subjectively, patients were evaluated via VAS scores, ODI scores, SF-36 scores, and Work Productivity and Activity Index. Treatment failures were defined as patients requiring post-treatment interventions at the disc level that was originally injected. Interventions included treatments such as discectomy, spinal fusion, disc replacement, or lumbar injections for anything other than imaging purposes [73].

Overall, researchers in this study determined that allogeneic MPCs were relatively safe with few notable adverse events reported. One patient in the 18 million MPC group experienced an exacerbation in their lower back pain that researchers considered was possibly related to the injection material but not necessarily the injection procedure itself. Additionally, another patient in the 6 million MPC group developed a post-treatment infection at the implant site. Overall, the patients in the 18 million MPC group registered the highest number of treatment-emergent adverse events (including increases in back pain, arthralgias, muscles spasms) out of all four study groups. Additionally, all four study groups maintained stable HLA classes I and II reactive antibody titers throughout the 3-year study period, with no statistically significant differences in donor-specific antibody response noted among all of the treatment groups [73].

In addition to the safety of allogeneic MPCs, Amirdelfan and colleagues assessed their efficacy in the management of back pain over the course of 3-year trial. Seventeen out of the 100 study subjects required post-treatment interventions and were thus considered treatment failures. Overall, the study group that received 18 million MPCs had significantly fewer subjects requiring a post-treatment intervention when compared to the saline group, and patients receiving 6 million MPCs demonstrated fewer post-treatment interventions than both the saline and HA groups. All four groups in the study demonstrated reduced VAS and ODI scores, with the MPC groups having overall moderately greater improvements in pain and disability when compared to the HA and saline groups. When correcting for post-treatment interventions, statistical analysis showed that patients in the 6 million MPC group had improved mean VAS scores when compared to the saline groups at 12, 24, and 36 months ($p=0.018$, $p=0.005$, and $p=0.047$). The 18 million MPC group also had improved mean VAS scores when compared to the saline group at 12, 24, and 36 months ($p=0.024$, $p=0.028$, and $p=0.006$). Analysis of median VAS scores, once adjusted for post-treatment interventions and non-responding patients, demonstrated that the median VAS scores for both treatment groups were also markedly improved from the initial baseline scores when compared to the saline and HA groups. MPC treatment groups furthermore demonstrated lower median

Table 2 Summary of clinical studies on the use of mesenchymal stem cells in the treatment of lower back pain

Study	Population	Treatment type	Outcome measures	Results	Conclusion
Kumar et al. (2017) [72] N=10 Follow-up=1 year Single arm phase-I clinical trial	10 patients with chronic lower back pain lasting for 3 months or more with a minimum 4/10 on VAS scale and ODI greater than or equal to 30%	Combination of hyaluronic acid (HA) and adipose tissue-derived mesenchymal stem cells (AT-MSCs) at a dose of 2×10^7 cells/disc (N=5) or 4×10^7 cells/disc (N=5)	VAS, ODI, SF-36, imaging (XR and MRI)	<ul style="list-style-type: none"> VAS, ODI, and SF-36 scores were lower in patients who received both high-dose and low-dose AT-MSC injections with no significant difference reported in the two groups Three of the six patients who reported improved VAS, ODI, and SF-36 scores demonstrated increased water content in their intervertebral discs on MRI No adverse events secondary to the transplants were noted in the 12-month study period 	The use of HA and AT-MSCs in management of patients with chronic discogenic lower back pain showed promising preliminary results and should be studied in a RCT with a larger sample size to increase validity
Noriega et al. (2017) [44] N=24 Follow-up=1 year Randomized control trial	24 patients with chronic back pain and lumbar degeneration unresponsive to prior treatment	Allogeneic bone marrow mesenchymal stem cells dosed at 25×10^6 MSC in 2 mL saline/segment	VAS, ODI, imaging (MRI)	<ul style="list-style-type: none"> Lumbar pain and disability were shown to be vastly improved 3 months post-transplant, and results were maintained throughout the 1-year follow-up period Patients in the control group receiving 2 mL of 1% mepivacaine had sharp decreases in pain at the 8-day follow-up visit, but they did not continue to have overall resolution of symptoms thereafter ODI values in the control group continued to increase at 3-, 6-, and 12-month follow-up appointments 	Allogeneic MSC therapy is a safe and efficacious alternative to autologous MSC treatment
Orozco et al. (2011) [48] N=10 Follow-up=1 year Pilot study	10 patients, male and female, with degenerative disc disease and persistent lower back pain for at least 6 months who had been nonresponsive to prior conservative treatments	Autologous mesenchymal bone marrow stem cells	VAS, ODI, MRI	<ul style="list-style-type: none"> No major adverse events were reported Patients demonstrated overall improvement in pain and disability approaching 71% optimal efficacy 85% of total improvement occurred within the first 3 months post-treatment 	MSC therapy is a viable alternative option in the treatment of chronic lower back pain

Table 2 (continued)

Study	Population	Treatment type	Outcome measures	Results	Conclusion
Anirdelfan et al. (2021) [73] N = 100 Follow-up = 3 years Multicenter, randomized, controlled study	100 patients diagnosed with chronic lower back pain with moderate degenerative disc disease at one level (L1-S1) lasting for at least 6 months and who had failed to achieve resolution of symptoms after 3 months of prior conservative treatments	Patients were randomized into four groups in a 3:3:2:2 ratio: 1) 6 million mesenchymal precursor cells (MPCs) with hyaluronic acid (HA) 2) 18 million MPCs with HA 3) HA vehicle control 4) Saline control (placebo)	VAS, ODI, SF-36, Work Productivity and Activity Index, imaging at 1, 3, 6, 12, 24, and 36 months	<ul style="list-style-type: none"> • 17 out of 100 patients required post-treatment interventions and were considered “treatment failures.” • Both MPC groups showed significant improvements in VAS and ODI scores when compared to the control groups • No significant changes in MP score on MRI were noted in all treatment groups over the 3-year study period • There was a low incidence of treatment-emergent adverse events with one patient demonstrating exacerbation of back pain that was possibly related to the injection and one patient developing an infection at the transplant site 	MPCs may provide a safe and effective means of treating patients with chronic lower back pain

ODI scores when compared to the saline and HA groups. However, in terms of radiologic assessment, no significant changes in the modified Pfirrmann (MP) scores on MRI were noted in any of the four study groups during the course of the trial. By the end of the study, the researchers concluded that allogeneic MPCs provide a safe, minimally invasive treatment option for chronic lower back pain sufferers who have failed prior conservative treatment options [73] (Table 2).

Future Clinical Studies

Given the preliminary evidence supporting both PRP and MSCs as viable treatment options, it is now incumbent upon the research community to further develop the therapeutics and techniques utilized in regenerative medicine. There are several registered clinical trials analyzing PRP or MSCs in the treatment of discogenic lower back pain. One study of note, currently in phase II, is comparing the use of PRP to bone marrow concentrate in patients with internal disc disruption (Table 3).

Classification System

Multiple classification systems for PRP usage having been proposed. One such classification is MARSPILL, based on method, activation, RBC, spin, platelets, image guidance, leukocytes, and light activation [31]. Another classification is based on different concentrations of components of the PRP (platelets, WBC, fibrin architecture), resulting in four types of PRP: pure PRP (no leukocytes, low-density fibrin network), pure platelet-rich fibrin (no leukocytes, high-density fibrin network), leukocyte-rich PRP (platelets and WBC in high concentrations, low-density fibrin network), and leukocyte- and platelet-rich fibrin (increased concentration of leukocytes, high-density fibrin network) [74, 75].

How Is It Used

With the range of spinal segment structures as possible sources of LBP, PRP sterile injection localization depends on the disease process being targeted [76], injecting the PRP under fluoroscopy focusing on either the disc nucleus [75, 77–81] or through intra-articular injection targeting either the sacroiliac joint [19, 20, 24] or the facet joints [81–84]. The injectable can be mixed with lidocaine and bupivacaine, either a single dose or double dose of PRP with a time interval in between [17, 20].

In multiple studies, interlaminar epidural injections of PRP directed into the affected nerve root area in patients with LBP seem to provide a gradual and sustained improvement of symptoms [81, 85]. After the injection, the patient should be observed for 15–20 min in supine position before discharge home [17].

Table 3 Ongoing clinical trials on the use of PRP, MSCs, and bone marrow concentrate in the treatment of chronic back pain

Phase	Identifier	Title	Estimated enrollment	Status
II	NCT04102761	Platelet rich plasma and bone marrow aspirate for lumbar intradiscal injections: a multicenter prospective randomized controlled trial in patients with internal disc disruption	60	Recruiting
IV	NCT04544709	Intradiscal platelet-rich plasma injection for chronic discogenic low back pain	100	Recruiting
IV	NCT03122119	Effectiveness of ultrasound guided platelet rich plasma injections in the sacroiliac joint to relieve low back pain	51	Active, not recruiting
IV	NCT04757740	Autologous platelet rich fibrin versus steroid in ultrasound-guided sacroiliac joint injection for joint dysfunction (randomized comparative study)	94	Not yet recruiting
II/III	NCT03737461	A phase 2/3 prospective, multicentre randomized, double-blind trial, comparing intra-discal allogeneic adult BM-MSc therapy and sham-treated controls in subjects with chronic LBP due to lumbar DDD unresponsive to conventional therapy	112	Recruiting
II	NCT04759105	Autologous mesenchymal stem/stromal cells for the treatment of workers affected by chronic low back pain due to multilevel intervertebral disc degeneration: a phase IIB randomized clinical trial	52	Recruiting
I	NCT04410731	CellKine: phase I study evaluating the safety and feasibility of allogeneic, culture-expanded bone marrow-derived mesenchymal stem cells in subjects with painful lumbar facet joint arthropathy	10	Recruiting
II	NCT04499105	Effectiveness and safety of allogenic mesenchymal stem cell (MSC) implantation on degenerative disc disease patients (clinical trial)	10	Recruiting
II/III	NCT04559295	Study of bone of marrow concentrate (BMC) injection in discs, facets, sacroiliac joints, and epidural space for chronic lower back pain with and without radiculopathy	80	Active, not recruiting

What Components Does PRP Contain?

To stimulate the recovery of tissues, PRP consists of autologous platelets being present in an increased concentration in a small suspension of plasma, having a “reversed” blood ratio: approximately 5% RBC, 94% platelets, and a small number of leukocytes [16, 17, 64, 79, 84, 86].

Platelets are the source of α -, δ -, and λ -granules, which are storage units for a wide range of components consisting of growth factors, chemokines, microparticles, and other bioactive molecules [11, 16, 17, 71, 86, 87]. Essential growth factors released from these granules are, among others, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), basic fibroblast growth factor (b-FGF), and insulin-like growth factor (IGF-1) [16, 17, 86, 88, 89].

How Is PRP Used in Back Pain?

With LBP having multiple possible causes, PRP has several target points in the body.

Various factors (nutritional, genetic, mechanical, biochemical) cause a shift towards catabolic metabolism of tissues, and it is this shift the PRP reacts on. Although an exact PRP action mechanism has not yet been universally

agreed upon, cellular and biochemical changes involved in mechanical structure and inflammation have been detected [15, 16].

These changes are induced by the growth factors released from the PRP, which play an essential role in their anti-inflammatory properties. PRP can stimulate cellular repair by increasing matrix synthesis and repair, nucleus pulposus survival, and cell proliferation. Promotion of angiogenesis results in increased blood flow and circulation to the tissue [15, 16, 90–93].

Inflammatory cytokines like TNF- α are linked to irreversible biomechanical and structural changes in bovine nucleus pulposus cells; PRP might ameliorate these changes by reducing the levels of TNF- α and IL-1 β gene expression and secretion. In osteoarthritis, PRP treatment led to an upregulated anabolic and downregulated catabolic gene expression, confirming that growth factors play an essential role in maintaining a balanced state between catabolic and anabolic processes [94, 95].

Discs are avascular structures with a limited nutrient supply [96]. This avascularity, especially in disc pathologies, is a challenge that can potentially be ameliorated by the introduction of VEGF, contained in PRP, stimulating angiogenesis [25, 26, 64, 96, 97].

In denaturated intervertebral discs, PRP injections can restore fluid flow capability and recover the mechanical properties of the discs [98]. PRP treatment creates a

supra-physiologic environment of growth factors, thereby supporting the healing process in chronic injuries [25].

Current ASIPP-Guidelines

The Patient

Patients are advised to pay attention to the following set of factors when considering a biologic therapy: the therapy-providing physician and facility, (non-) credible medical claim, FDA/abroad equally qualified organizations' approval, presence of shared-decision making, and informed consent [64].

Legal

Current ASIPP-Guidelines state that next to a discussion about risks and benefits of and inclusion and exclusion criteria for the treatment, a consent form should be discussed and signed by both the patient and the provider of the PRP-therapy [64]. Exclusion criteria would include several contraindications, among which, but not limited to, anemia, fever, hematologic blood dyscrasias, malignancy, or unrealistic expectations [64].

PRP material should follow FDA guidelines and be at least 2.5 times greater than baseline plasma concentration [86]. Before injection, verification of patient, PRP material, injection location, and side should occur; direct visualization with image guidance is recommended for injections [64]. After the injection, patients should rest and (partially) immobilize the injected body part for up to 2 weeks, not use anti-inflammatory medications for at least multiple weeks; both verbal and written instructions (including red flags) should be given to both the patient and caretaker and follow-up should take place every 2 to 4 weeks till a clear demonstration of a significant improvement in pain and function [64].

Dependent on the situation, repeat injections may be necessary, considering all possible causes of this necessity. The patient's repeated imaging is not recommended unless changes in the patients' situation (pathology, symptoms) indicate so [64].

Following both national and musculoskeletal interventional pain management guidelines and taking into account the lower costs of corticosteroid injections compared to PRP for chronic conditions of joint degeneration, PRP is, for now, considered when corticosteroids are no longer appropriate for a patient or failed as a treatment. Guiding Principles of the WHO encourage collecting global information regarding safety and

adverse reactions of biological products and the registry of its providers and users [99].

Conclusion

The strengths and limitations of biologics in the treatment of musculoskeletal injuries and LBP continue to be discovered. Current treatments for chronic back pain include conservative management with exercise, medications such as NSAIDs, surgical fusions, radiofrequency ablation, and spinal cord stimulation, among others. Conservative management continues to be the first-line treatment for LBP. Once conservative options have failed, other treatments have been shown to be effective but also come with considerable side effects and complications. Due to the cost associated with managing these complications, further investigation of alternate treatments remains prudent.

PRP and MSCs are used autogenously to help facilitate the healing process, and their injection has been studied in long-term management of discogenic low back pain. PRP has been compared to steroid injections in the sacroiliac joint for chronic LBP, with favorable results. MSCs have also been shown to be useful in intervertebral disc regeneration and treatment of chronic LBP associated with degenerative disc disease.

As it currently stands, the price for these treatments is still too high, and thus the standard of care continues to be steroid injections and other treatments. Biologics are often indicated for those who fail corticosteroids or for whom they are no longer appropriate. This could change, however, with more robust data and research on safety and long-term efficacy of biologics compared to other interventional management.

Biologics are considered by many to be an economic and fast treatment option, especially for those that fail standard of care treatments. The survival and evolution of biologics into a routine clinical treatment option depend on the standardization of their use, consistency of outcomes, and a decrease in overall healthcare costs. Further high-quality studies can aid in this goal by providing more data and providing more predictability in the use of biologics. This will require commitment from all levels of participants to better utilize biologic therapies and regenerative medicine going forward.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent No human or animal subjects were included in this paper. there is no new data in this paper, this is a review of existing published articles.

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

Authors and Affiliations

Alan D. Kaye¹ · Amber N. Edinoff² · Yale E. Rosen³ · Megan A. Boudreaux³ · Aaron J. Kaye⁴ · Meeta Sheth¹ · Elyse M. Cornett^{1,9}  · Vanessa Moll^{5,6} · Claudia Friedrich⁵ · Johan Sibrecht Verhagen⁵ · Berthold Moser^{7,8} · Annu Navani^{8,9,10}

✉ Elyse M. Cornett
elyse.bradley@lsuhs.edu

¹ Department of Anesthesiology, Louisiana State University Health Shreveport, 1501 Kings Highway, Shreveport, LA 71103, USA

² Department of Psychiatry, Massachusetts General Hospital, Harvard School of Medicine, Boston, MA 02114, USA

³ School of Medicine, Louisiana State University Health Shreveport, Shreveport, LA, USA

⁴ Department of Anesthesiology and Perioperative Medicine, Medical University of South Carolina, Charleston, SC 29425, USA

⁵ Department of Anesthesiology, University Hospital Zürich (USZ), Zurich, Switzerland

⁶ Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA

⁷ Department of Anesthesia and Intensive Care, Medical University Innsbruck, Innsbruck, Austria

⁸ Department of Anesthesiology and Intensive Care Medicine, See-Spital, Horgen, Switzerland

⁹ Medical Director, Comprehensive Spine and Sports Center, Campbell, CA and Advisor, Le Reve Regenerative Wellness, Campbell, CA, USA

¹⁰ Comprehensive Spine and Sports Center, 3425 S Bascom Ave #200, Campbell, CA 95008, USA