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# CellKine clinical trial: first report from a phase 1 trial of allogeneic bone marrow–derived mesenchymal stem cells in subjects with painful lumbar facet joint arthropathy

Dan Yan[a], Abba C. Zubair[b], Michael D. Osborne[a], Robert Pagan-Rosado[a], Jeffrey A. Stone[c], Vance T. Lehman[d], Nisha C. Durand[b,e], Eva Kubrova[f], Zhen Wang[g,h], Drew M. Witter[i], Meghan M. Baer[h], Gabriela C. Ponce[h], Alfredo Quiñones-Hinojosa[j], Wenchun Qu[a,e,*]

**Abstract**

**Background:** Lumbar facet joint arthropathy (LFJA) is a major cause of low back pain (LBP), with current treatments offering limited long-term benefits. Bone marrow–derived mesenchymal stem cells (BM-MSCs) show promise due to their immunomodulatory and trophic effects, potentially addressing underlying degenerative processes in LFJA.

**Objectives:** This initial report describes the outcomes of the first treated patient in an ongoing mutidisciplinary phase 1 clinical trial evaluating the safety and feasibility of intra-articular allogeneic BM-MSCs for painful LFJA.

**Methods:** Following enrollment in our IRB-approved protocol, symptomatic LFJA was confirmed through double blocks on L4 and L5 medial branches. Two 1-mL syringes, each containing 10 million BM-MSCs, were prepared in the cGMP facility and administered bilaterally to the patient's L4-L5 lumbar facet joints. The patient underwent standardized follow-ups, including clinical examinations and functional and imaging assessments for 2 years, utilizing patient-reported outcomes measurement information system—computer adaptive tests (PROMIS CATs), visual analogue scale, Oswestry disability index, work functional status and opioid pain medication use, and MR imaging Fenton–Czervionke score.

**Results:** The patient tolerated the procedure well, with no drug-related adverse events during the study period. Pain, spine function, and work functional status improved at multiple follow-ups. This patient also reported improvements in mental and social health, along with a notable improvement in the grade of facet synovitis observed at the one-year follow-up MRI evaluation.

**Conclusions:** This case report suggests the safety and feasibility of administering intra-articular allogeneic BM-MSCs, offering therapeutic benefits for pain management and functional activities.

**Keywords:** Clinical trial, BM-MSCs, Bone marrow–derived mesenchymal stem cells, LBP, Low back pain, LFJA, Lumbar facet joint arthropathy, Musculoskeletal disorders, Pain management

## 1. Introduction

Low back pain is a common musculoskeletal condition with a prevalence of 84% in the adult population.[18] It is the leading cause of disability worldwide and places a heavy economic burden on the healthcare system, exceeding 500 billion dollars per year in the United States.[18,33] In many cases, LBP is multifactorial involving facet joints, spinal ligaments, spinal nerve roots, spinal musculature, or intervertebral disks.[34] Lumbar facet

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*[a] Department of Pain Medicine, Mayo Clinic, Jacksonville, FL, USA, [b] Transfusion Medicine, Department of Pathology, Mayo Clinic, Jacksonville, FL, USA, [c] Department of Radiology, Mayo Clinic, Jacksonville, FL, USA, [d] Department of Radiology, Mayo Clinic, Rochester, MN, USA, [e] Center for Regenerative Biotherapeutics, Mayo Clinic, Jacksonville, FL, USA, [f] Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA, [g] Evidence-Based Practice Center, Mayo Clinic, Rochester, MN, USA, [h] Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, USA, [i] Center for Clinical and Translational Science, Mayo Clinic, Rochester, MN, USA, [j] Department of Neurosurgery, Mayo Clinic, Jacksonville, FL, USA*

**Corresponding author. Address: Department of Pain Medicine, Mayo Clinic, 4500 San Pablo Rd S, Jacksonville, FL 32224. Tel.: 904 953 7246. E-mail address: Qu.Wenchun@mayo.edu (W. Qu).*



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joint arthropathy (LFJA) is one of the major causes of low back pain (LBP) with an estimated prevalence of 15% to 40% among patients with LBP.[20]

Lumbar facet joints are synovial joints and are structurally made up of cartilage, articular capsule, and synovium. They are part of the 3-joint complex or spinal motion segment, which is composed of one intervertebral disk and 2 paired-facet joints. Its functions are to facilitate flexibility and movement of the spinal column.[24,26] Lumbar facet joint arthropathy is a broad term that encompasses age-related, degenerative, and proliferative changes including the narrowing of joint spaces, subarticular bone erosions, subchondral cysts, osteophyte formation, and hypertrophy of the articular processes.[24] Facet joints possess similar anatomical characteristics and share common pathophysiological processes as in osteoarthritis of other synovial joints such as the hip and knee.[23,24,26] Pain is the most noticeable symptom of LFJA. The prevalence of LFJA decreases in the upper lumbar regions, with levels of L4-L5 being the most commonly affected, followed by L5-S1 and L3-4.[32] Patients with LFJA experience an exacerbation of symptoms with lumbar extension, extension-rotation, side bending, and palpation over the affected facet joint which can be unilateral or bilateral. The pain can manifest in both axial and referral patterns, without significant radiation beyond the knee.[24,26,32]

Current treatments for symptomatic LFJA include oral analgesics, physical therapy, and image-guided interventional procedures such as corticosteroid injections, medial branch nerve blocks, medial branch rhizotomy, and platelet-rich plasma injections.[11,36] Corticosteroid injections tend to offer short-term pain relief with mixed evidence for long-term efficacy.[50] Radiofrequency ablation has been shown to provide an average of nine months of pain relief but with an associated risk of multifidus denervation and subsequent atrophy.[15,20] Most of the aforementioned treatments only focus on symptomatic relief without addressing the underlying pathophysiology to slow or halt the degenerative process. They have also met with challenges of lacking long-term effectiveness.[7]

Mesenchymal stem cells, also known as mesenchymal stromal cells or medicinal signaling cells (MSCs), have attracted significant interest in the treatment of symptomatic synovial joint degeneration due to their immunomodulating effect and low immunogenicity.[7,12] Prospective studies investigating the safety of BM-MSC treatment in human subjects have not identified any serious adverse events resulting directly from treatment when BM-MSCs were delivered intra-articularly to the knee.[1,21,27,35,37,43,47,48] However, the role of BM-MSCs in treating patients with LFJA has not been thoroughly studied. This case report presents the initial results for the first patient enrolled in CellKine, a phase 1 clinical trial of allogeneic culture-expanded BM-MSCs for the treatment of painful lumbar facet arthropathy (Mayo Clinic IRB#: 20-000330; ClinicalTrials.gov Identifier: NCT04410731).

## 2. Methods

### 2.1. Case presentation

The patient is a 61-year-old woman with a past medical history of peripheral neuropathy, asymptomatic coronary artery disease, hypertension, hyperlipidemia, gastroesophageal reflux disease, osteoarthritis in multiple joints, and depression who experienced low back pain for more than 3 years. The pain was described as 8 out of 10 on the visual analogue scale (VAS) at the screening visit. It was exacerbated by bending the lumbar spine backward and engaging in vigorous physical activities. She did not recall any precipitating event such as a fall or traumatic event. She did not experience long-term benefits from her previous back pain care, including several facet medial branch radiofrequency ablations (bilateral L3-L4 and L4-L5 levels), facet joint corticosteroid injections (bilateral L3-L4 and L4-L5 levels), physical therapy exercises, and transcutaneous electrical nerve stimulation (TENS). Physical examination was positive for bilateral lower lumbar facet loading maneuvers and lower lumbar paraspinal tenderness. Her lumbar *MRI* indicated advanced degenerative disk changes and facet arthropathy (FA) across multiple levels. Specifically, moderate FA was present with suspected bilateral facet synovitis at L3-L4 while severe FA was noted at L4-L5 with severe right-sided facet synovitis.

### 2.2. Product preparation and administration

Following informed consent, symptomatic LFJA was confirmed through double blocks on L4 and L5 medial branches, yielding positive outcomes of over 75% pain alleviation. Bone marrow–derived mesenchymal stem cells were isolated from a healthy 28-year-old female donor, culture-expanded, cryopreserved, and stored in vapor phase liquid nitrogen (less than −150°C). Quality control testing was performed on the final cryopreserved cell product before release, with the testing results of expressing CD105, CD73, and CD90 (95.52% positive), lacking expression of CD45, CD34, CD11b, CD19, and HLA-DR (2.04% positive), cell viability of 93.18%, endotoxin level of <0.550 EU/mL, mycoplasma negative and no microorganism growth after 14 days (sterility testing). On the day of infusion, the final cryopreserved Passage 3 BM-MSCs were thawed and reformulated in Lactated Ringer's solution at a concentration of 10 million cells/mL. Two 1-mL syringes, each containing 10 million BM-MSCs, were prepared in the curent good manufacturing practice (cGMP) facility and then kept refrigerated (2–8°C) for intra-articular facet injection using standard techniques under local anesthesia with 1% lidocaine, fluoroscopy guidance, and contrast (Omnipaque 180).

### 2.3. Outcome measures

Per protocol, the patient was evaluated at the screening/pre-injection visit (baseline), injection visit, and standardized follow-ups scheduled on day 1, day 3 to day 5, week 2, month 3, month 6, month 12, month 18, and month 24. a neuromusculoskeletal physical examination (PE), and clinical assessments of low back pain and function as reflected by validated outcome measures (patient-reported outcomes measurement information system—computer adaptive tests [PROMIS CATs], VAS and Oswestry disability index [ODI]),[4,8,10,13,22,28,43] lumbar spine radiographs, blood sample analysis (complete blood count, C-reactive protein, cholesterol, activated partial thromboplastin time, prothrombin time, chemistry liver, and renal function) for safety surveillance, and lumbar spine MRI (fat-suppressed T1 and T2-weighted image without contrast). The patient was assessed for the occurrence of any acute, subacute, or chronic adverse events throughout the entire study of 2 years. Blood sample analysis, PE, and lumbar spine MRI were performed at 3-, 12-, and 24-month follow-ups.

## 3. Results

### 3.1. Safety and adverse events

The patient tolerated the procedure well and did not experience any serious adverse events. She reported dull pain radiating from

the waistline to her buttocks one day after the intra-articular BM-MSC injection which gradually resolved with Tylenol and other conservative management within 9 days. Throughout the 24-month follow-up period, the patient reported some other AEs including bruising below the injection site, rash on the face, diarrhea, trochanteric bursitis, chest discomfort, narrow angles after laser peripheral iridotomy, shoulder pain, hysterectomy, urinary tract infection, superficial basal cell carcinoma, and recurrent depressive disorder. None of them was related to the investigational drug.

### 3.2. Visual analogue scale, Oswestry disability index, and patient-reported outcomes measurement information system—computer adaptive tests

The patient's back pain, physical function, and mental and social well-being were assessed using VAS, ODI, and 7 domains of PROMIS CATs incldiuing physical function (PF), pain interference (PI), anxiety, depression, fatigue, sleep disturbance, and social function. For PROMIS CATs, a higher score signifies a greater manifestation of the concept being measured.[4] In this trial, a 50% reduction in low back pain (VAS),[3] improvement of 15 points in ODI[16] or 2.3 points in PROMIS PF[31] were considered as the minimum clinically important difference (MCID) thresholds.

Continuous back pain relief was observed on VAS, with a 7.1-point decrease from baseline to 24 months. The patient responded to the MCID at 6, 12, 18, 24 months. A progressive improvement in spinal function was noted as reflected by the ODI score from 3 to 5 days to 6 months, with the patient responding to the MCID at 3, 6, 12, 18, and 24 months. For the PROMIS PF, it significantly improved by 9 points from baseline to 24-month follow-up, with a consistent improvement of 16 points sustained up to 12 months. The MCID was met at 3- to 5-day, 2-week, 3-. 6-, 12-, 18-, and 24-month follow-ups, **Figure 1** and **Table 1**.

Improvements in PI were noted at various follow-ups, with a notable increase of 29 points observed at 12 months. Regarding the ability to participate in social roles and activities, there was a significant increase of 18 points observed at 24 months, with a progressive improvement of 28 points noted up to 18 months following the injection. Addtionally, significant improvements of 16 points and 8 points were noted at 24 months in anxiety and depression, respectively. Similarly, improvements were observed in sleep disturbance and fatigue with increases of 12 and 6 points, respectively, **Figure 2** and **Table 1**.

### 3.3. Work functional status questionnaire and opioid pain medication use

A substantial improvement in work functional status, referring to the physical capability to perform the regular job tasks, was observed at the 3-month follow-up. The patient reported that she could perform all necessary tasks at work and as much work as she wanted from the 6-month through the 24-month follow-ups, **Table 1**. She reported taking opioids for her knee arthroplasty in October 2019 before her enrollment but was not actively using any opioids at the time of her enrollment or during the study period.

### 3.4. Magnetic resonance imaging

The extent of facet synovitis was graded using the method described by Fenton and Czervionke.[17] There was a significant imaging improvement of the right L4-L5 facet joint, progressing from grade 4 synovitis at baseline to grade 1 at 12-month and 24-month follow-ups. Two Dixon sagittal and axial MRI images of the right L4-L5 facet joint were captured before the injection (**Fig. 3A, B**) and at 12 months postinjection (**Fig. 3C, D**). In addition, mild grade 1 synovitis was observed at baseline in the left L3-4 facet joint, which improved at 12-month follow-up. The L3-L4 facet was not treated in this study period. Throughout the study period, stable, mild osteoarthritic changes were noted in the bilateral L4-L5 facet joints, **Table 2**.

## 4. Discussion

The pathophysiology of LFJA is complex and oftentimes linked with degenerative disk disease (DDD).[9] Studies suggest that disk degenerative changes with loss of disk height result in increased mechanical load of the facet joints.[9,45] Hyaline cartilage degradation and synovial membrane inflammation contribute to subchondral bone sclerosis, osteophyte formation, and cyst growth that are most common presentations.[7] On MRI imaging, there is a thin, triangular synovial membrane along the inner margin of the joint capsule at the anteroposterior and poster-oinferior margins of the facet joint.[50]

The synovium may become inflamed as degenerative changes of the cartilage extend to the synovium.[2] The secondary edema frequently involves the attached fibrous connective tissue making up the facet joint capsule and extends to varying degrees to involve the adjacent periarticular fat and muscle, ligamentum flavum, and

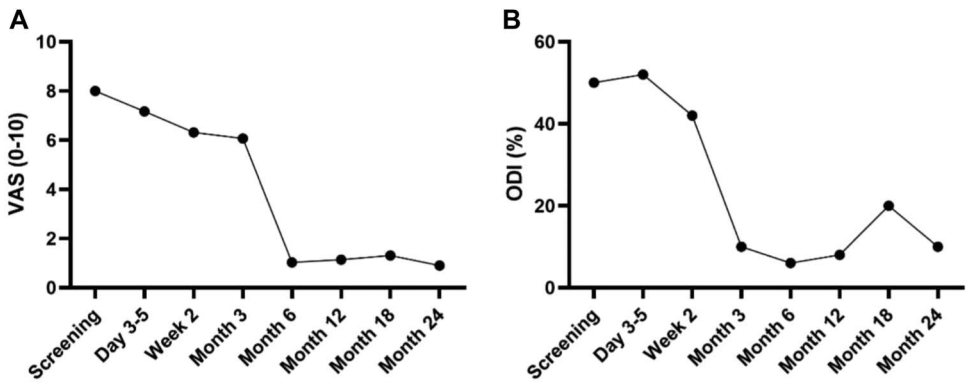


Figure 1. The changes in VAS and ODI scores over a 24-month study period. (A) Progressive pain relief was observed in the VAS score. The score ranges from 0 to 10, with 10 being the worst imaginable pain and 0 being no pain. The MCID was reached at 6, 12, 18, and 24 months. (B) ODI score progressively improved from 3 to 5 days to 6 months, and the patient responded to the MCID at 3, 6, 12, 18, and 24 months.

**Table 1**

**Visual analogue scale, Oswestry disability index, patient-reported outcomes measurement information system—computer adaptive test scores and work functional status at all follow-ups.**

| | Screening | Day 3-5 | Week 2 | Month 3 | Month 6 | Month 12 | Month 18 | Month 24 |
|---|---|---|---|---|---|---|---|---|
| **VAS (0-10)** | 8 | 7.17 | 6.31 | 6.07 | 1.03 | 1.14 | 1.31 | 0.9 |
| **ODI (0-100)** | 50 | 52 | 42 | 10 | 6 | 8 | 20 | 10 |
| **PROMIS CATs (10-90)** | | | | | | | | |
| Physical function | 29 | 32 | 32 | 40 | 45 | 45 | 43 | 38 |
| Pain interference | 69 | 73 | 67 | 56 | 40 | 40 | 49 | 60 |
| Ability to participate social roles and activities | 37 | 35 | 37 | 52 | 58 | 60 | 65 | 55 |
| Anxiety | 65 | 49 | 46 | 74 | 48 | 67 | 54 | 49 |
| Depression | 58 | 58 | 48 | 75 | 50 | 58 | 50 | 50 |
| Sleep disturbance | 62 | 62 | 62 | 65 | 62 | 50 | 46 | 50 |
| Fatigue | 49 | 57 | 49 | 66 | 43 | 59 | 43 | 43 |
| **Work functional status** | | | | | | | | |
| Could do limited/restricted work? | Cannot do my usual work | Hardly do any work at all | Cannot do my usual work | Do most of my usual work, but no more | Do as much work as I want to | Do as much work as I want to | Do as much work as I want to | Do as much work as I want to |

Work functional status, physical capability to perform regular job tasks.

ODI, Oswestry disability index; PROMIS-CATs, patient reported outcomes measurement information system—computer adaptive tests; VAS, visual analog scale.

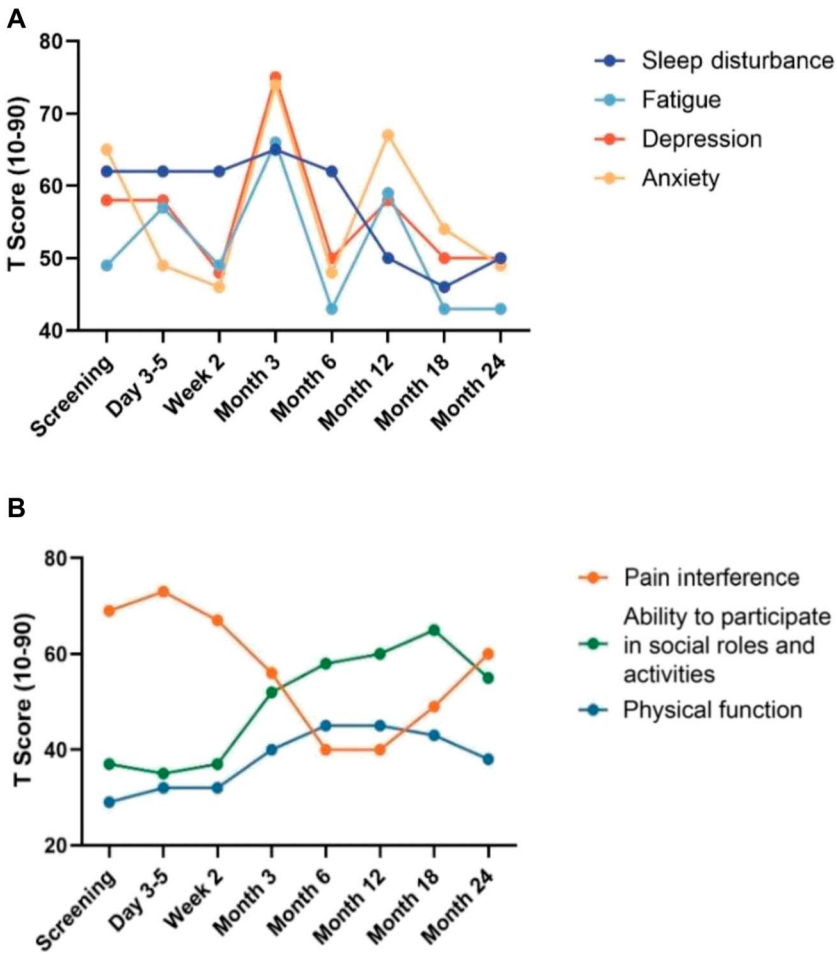


Figure 2. The changes in PROMIS CAT T scores for spine function, mental, and social well-being throughout this study. (A) A higher score indicates poorer sleep quality, higher levels of fatigue, and greater psychological distress. The decreasing scores signify improvements. (B) A higher score of pain interference indicates more pain-related interference with no observed improvement. Conversely, a higher score of physical function and ability to participate in social roles and activities suggests better physical function and greater ability for social activities, with improvements observed.

**Table 2**

**Fat-suppressed T2-weighted magnetic resonance imaging evaluation at screening, 3 months, 12 months, and 24 months.**

| | Disk level | Screening | Month 3 | Month 12 | Month 24 |
|---|---|---|---|---|---|
| MR imaging Fenton–Czervionke score | Right L3-4 | 0 | 0 | 0 | 0 |
| | Right L4-5 | 4 | 4 | 1 | 1 |
| | Right L5-S1 | 0 | 0 | 0 | 0 |
| | Left L3-4 | 1 | 1 | 0 | 0 |
| | Left L4-5 | 0 | 0 | 0 | 0 |
| | Left L5-S1 | 0 | 0 | 0 | 0 |

0, No signal abormality; 1, signal abnormality confined to the joint capsule; 2, periarticular signal abnormality involving less than 50% of the perimeter of the joint, 3, periarticular signal abnormality involving more than 50% of the perimeter of the joint, 4, grade 3 with the extension of signal abnormality into the intervertebral foramen, ligamentum flavum, pedicle transverse process, or vertebral body.

foraminal epidural fat and may also be associated with pedicle, transverse process, and vertebral body bone marrow edema. This is easily detectable on T2-weighted MRI sequences. The Fenton and Czervionke grading system for MRI was introduced to assess the extent of synovitis present on T2-weighted and postcontrast spine imaging. The presence and side of facet-mediated pain were further correlated with the presence of synovitis.[17]

Regenerative medicine is an emerging interdisciplinary approach that is progressively gaining traction in the realm of musculoskeletal conditions. Innovative treatment options, often referred to as orthobiologics, encompass techniques such as platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), micro-fragmented fat (MFAT), as well as exosomes or MSCs.[33,40] Cell-based therapies, particularly notable for their robust immunomodulatory and trophic effects, stand out as promising contenders and have been extensively employed in addressing degenerative conditions like knee osteoarthritis.[7]

Mesenchymal stem cells can be harvested from a variety of sources including adipose tissue, bone marrow, umbilical cord or blood, menstrual blood, and others.[46] Among them, bone marrow is the most frequently used.[5] The necessity of allogeneic MSC transplantation is called upon with the advantages of off-the-shelf availability, lower cost, and greater quantities.[52] Previously completed clinical trials have demonstrated encouraging results in evaluating the safety and efficacy of BM-MSCs for the treatment of knee and hip joint osteoarthritis, which suggests a safety profile of MSC transplantation in synovial joints.[6,7,14,19,29,38,39,41] In addition, other studies reported the safety and feasibility of BM-MSCs for treating axial low back pain with significant pain and functional improvements.[6,14,29,39,41] With regard to the treatment of painful facet arthropathy, there is a paucity of evidence on safety and efficacy with the use of injectable orthobiologics. Most of the currently available positive studies focus on PRP injections. A prospective randomized controlled study demonstrated sustained significant improvements in VAS, and ODI at 6 months when comparing PRP with corticosteroid injections.[19,51] Nonetheless, there are a few level-1 studies evaluating the safety and efficacy of PRP on facetogenic

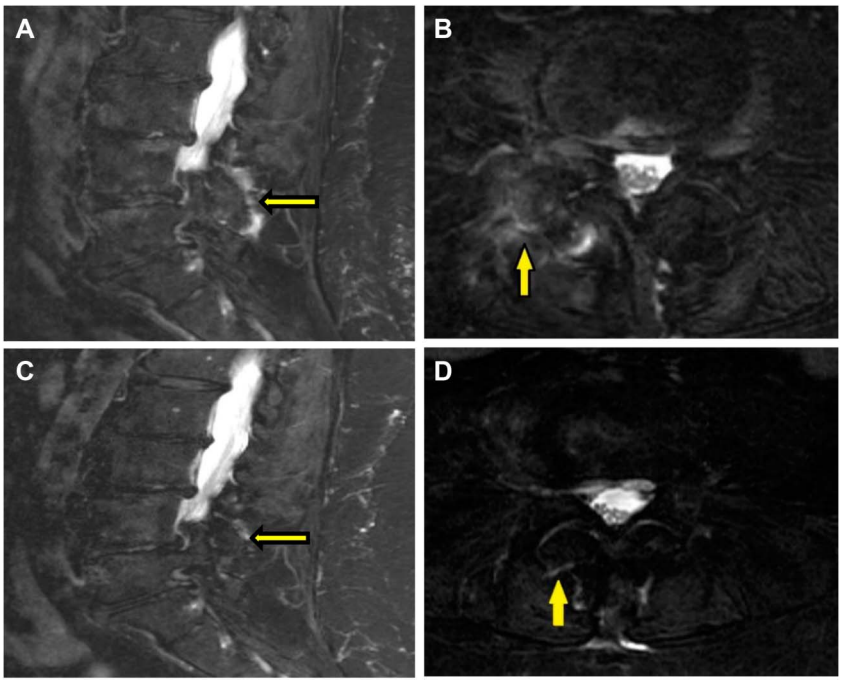


Figure 3. Two Dixon sagittal and axial MR images of the right L4-L5 facet joint were captured before the BM-MSC injection (A and B) and at 12 months postinjection (C and D). In images (A) and (B), abnormal increased signal (edema) involving the posterior facet joint capsules (yellow arrows) was observed, with lateral extension along the margin of the joint into the right L4-L5 neural foramen, as well as edema of the right ligamentum flavum consistent with grade 4 facet synovitis. In images (C) and (D), a reduction of edema involving the facet joint capsule was observed, with the focal residual abnormal signal at the posterior margin of the synovial capsule consistent with grade 1 facet synovitis.

pain, nor are there studies showing outcomes beyond the 12-month mark.[19] This case report adds valuable data that can be utilized as the foundation to expand current knowledge on cell-based therapy in the treatment of axial low back pain, specifically painful LFJA.

This case report provides insights into our initial experience with intra-articular facet BM-MSC injection, focusing on safety and feasibility. Apart from the expected adverse events such as short-lived tightness and pain at the injection site following the procedure, no agent-related adverse events occurred throughout the study period. The patient responded to MCIDs for VAS, ODI, and PROMIS PF at multiple follow-ups. In addition, the patient reported improvements in sleep and mental and social well-being, which are commonly associated with pain relief and improved spinal function, thereby contributing to higher satisfaction with social functioning and sleep quality.[25,30,44] During the 3-month follow-up, a temporary sharp increase in psychological distress was reported, likely attributable to her family member being diagnosed with cancer.[49] Furthermore, this patient had a significant decrease in the grade of facet synovitis at the one-year follow-up MRI evaluation. Particularly, the treated right L4-L5 facet showed minimal residual facet synovitis, improving from grade 4 to grade 1, which interestingly had a greater right-sided component of pain at initial presentation. This notable imaging finding suggests a reduction of inflammatory processes in the facet synovium, which is consistent with the immunomodulatory function of MSCs. While the untreated grade 1 facet synovitis involving the left L3-L4 facet joint also improved, this improvement may be attributed to the pain relief and enhanced spine function contributing to improved biomechanics. Although this information is limited to one patient, it instills confidence in evaluating the effectiveness of the BM-MSC treatment strategy for patients with painful LFJA.

## 5. Conclusion

This case report suggests a promising outlook regarding the safety and feasibility of administering intra-articular allogeneic BM-MSCs, along with therapeutic advantages for pain management and functional activities. As the trial progresses, our understanding will continue to expand. However, the scarcity of numerous high-quality studies (levels 1 and 2) hampers the broad adoption of BM-MSCs as a treatment for painful lumbar facet joint arthropathy, aligning with other emerging orthobiologic interventions. To establish the safety and efficacy of this therapeutic approach for patients with painful LFJA, it is imperative to conduct larger, meticulously designed randomized controlled trials in the future.

## Disclosures

A.Q. is the founder of DOME Therapeutics. The other authors indicated no conflicts of interest.

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Ethical approval and consent to participate: This study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of Mayo Clinic, FL (Mayo Clinic IRB#: 20-000330). This clinical trial was also registered on ClinicalTrials.gov with the identifier of NCT04410731 (https://clinicaltrials.gov/study/NCT04410731). Before participation, written informed consent was obtained from the patient.

Consent for publication: Not applicable.

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