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Combined Subchondral, Intradiscal and Peridiscal BMAC Injections for Advanced Degenerative Discs and Endplates with Modic Changes: Retrospective Pilot Case Series

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Background: Degenerative disc disease (DDD) with cartilaginous endplate degeneration and Modic type 1 or 2 changes is increasingly recognized as a source of chronic vertebrogenic and discogenic low back pain. Because the intervertebral disc and vertebral endplates function as a biological and biomechanical unit, regenerative strategies targeting both structures may better address the disc-endplate complex.

Case Series: Thirteen consecutive patients with chronic refractory vertebrogenic and/or discogenic low back pain, MRI evidence of DDD with Modic type 1 or 2 changes, and failure of conservative management underwent combined intradiscal, peridiscal, and subchondral bone marrow aspirate concentrate (BMAC) injections under fluoroscopic guidance. Four patients had previously undergone basivertebral nerve radiofrequency ablation. The cohort included 6 men and 7 women with a mean age of 56.2 ± 17.5 years. Follow-up ranged from 4 to 15 months. Mean Visual Analog Scale scores decreased from 7.3 ± 2.0 at baseline to 2.1 ± 1.6 at latest follow-up, a mean reduction of 5.2 ± 1.8 points (72.7% ± 19.5%). All patients achieved at least 50% pain reduction and reported functional improvement. Twelve patients (92.3%) were satisfied or very satisfied, and all would recommend the procedure. No major procedure-related complications were observed.

Conclusion: Combined intradiscal, peridiscal, and subchondral BMAC injections were associated with substantial pain reduction, functional improvement, high patient satisfaction, and no major complications in this small retrospective case series. Larger prospective controlled studies are needed to confirm these preliminary findings.

Key words: Vertebrogenic pain; discogenic pain; degenerative disc disease; Modic changes; bone marrow aspirate concentrate; mesenchymal stem cells; subchondral injection

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BACKGROUND

Degenerative spine disease is one of the most prevalent causes of chronic vertebrogenic and discogenic pain, representing a major source of disability worldwide (1). Progressive degenerative disc disease may result in structural damage of the intervertebral disc and adjacent vertebral cartilaginous endplates (CEPs), which can lead to inflammation, impaired nutrient diffusion, and altered biomechanics, ultimately resulting in chronic axial low back pain that is often refractory to conventional management (2-4).

Modic changes and endplate defects are increasingly recognized as critical pain generators for chronic axial low back pain (5). Inflammatory mediators released from the disc and degenerated endplates propagate nociceptive signaling and accelerate disc and CEP degeneration (6,7). This pathophysiological interplay between disc, endplate, and the subchondral bone has led to a paradigm shift from purely mechanical explanations of low back pain toward a more integrated biomechanical model.

Regenerative injection therapies, particularly the use of bone marrow aspirate concentrate (BMAC) rich with mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), and α2-macroglobulin (A2M), have emerged as promising biologic strategies to modulate inflammation and immune response, and to promote tissue repair (8,9). By delivering trophic and anti-inflammatory cytokines, as well as progenitor cells capable of chondrogenic and angiogenic differentiation, BMAC-MSCs may restore the microenvironment of the disc–endplate complex and slow the degenerative cascade (4).

Subchondral injections of BMAC-MSCs, combined with peridiscal and intradiscal delivery, are designed to target the multifactorial origin of chronic axial pain. These techniques aim to restore structural integrity of the vertebral endplates, reduce neuroinflammation, and enhance disc nutrition (4). Prior studies in musculoskeletal medicine, particularly in osteoarthritis of the knee and hip, have demonstrated that combined subchondral and intra-articular biologic injections result in greater and more durable improvements than single-compartment approaches (10,11).

Building upon this scientific rationale, we present our retrospective case series of 13 patients with chronic refractory vertebrogenic and discogenic axial low back pain treated with combined intradiscal, peridiscal, and subchondral BMAC-MSC injections. The purpose of this investigation, therefore, is to describe the procedural technique, to report clinical outcomes, and to explain the biological rationale supporting the inclusion of subchondral targets in regenerative injection therapies for the management of the degenerative spine with biologics.

METHODS

Study Design and Patient Selection

The present investigation was a retrospective medical record review of 13 consecutive patients with chronic refractory vertebrogenic and/or discogenic axial low back pain treated at Advanced Spine on Park Avenue, New York and the EuroPainClinics, Slovakia, between September 2024 and December 2025.

Inclusion Criteria:

- Chronic axial low back pain (>6 months) associated with self-reported functional limitations affecting daily activities, with or without radicular symptoms.
- Magnetic resonance imaging (MRI) evidence of degenerative changes, including multilevel Modic type 1 or 2 endplate changes and multilevel disc degeneration (Fig. 1).
- Failure of conservative therapies such as pharmacologic management, physical therapy, and interventional procedures (facet joint injections, epidural steroid injections, or radiofrequency ablation).

Exclusion Criteria:

- Patients with evidence of spinal infection, malignancy, or systemic inflammatory disease were excluded.

All patients provided written informed consent before undergoing biologic treatment. The study protocol, including the retrospective review of patients treated at both EuroPainClinics in Slovakia and Advanced Spine on Park Avenue in New York, was reviewed and approved by the Ethics Committee of the Košice Self-governing Region, Slovak Republic (Approval No. 10148/2024/ODDZ-44592). The study was conducted in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

Procedure Details

Patient Consent and Preparation

Prior to the procedure, all patients were thoroughly informed about the risks, benefits, and alternatives of the procedure and BMAC therapy. Potential complications were discussed, including infection, bleeding, nerve or spinal cord injury, discitis, and the possibility of a lack of clinical improvement.

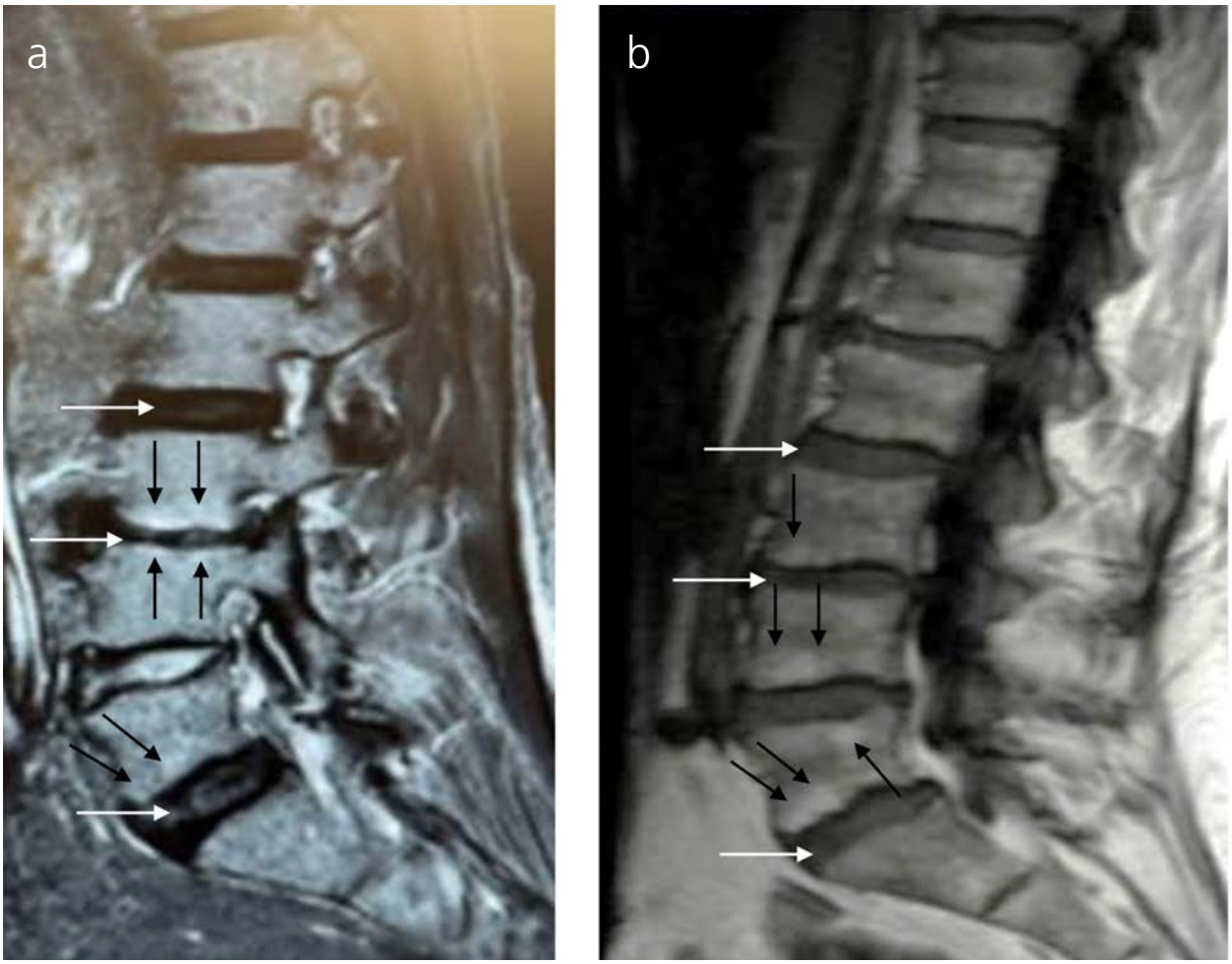

Fig. 1. Lumbar spine MR images demonstrating degenerative disc disease (white arrows in a and b) and degenerative endplate (Modic) changes (black arrows in a and b). Sagittal STIR (a) and T1-weighted (b) images demonstrate multilevel degenerative disc disease characterized by disc height loss and endplate irregularities, with associated Modic type 1 and type 2 endplate changes consistent with vertebrogenic and discogenic pain generators.

All patients presented with chronic vertebrogenic and/or discogenic low back pain associated with multilevel DDD and Modic type 1 or 2 changes. All patients had failed to achieve sustained pain relief from prior conservative or interventional treatments. Surgical options were offered, although all patients declined surgery and elected to undergo combined intradiscal, peridiscal, and subchondral (intraosseous) BMAC-MSC injections.

To optimize biologic response, patients were instructed to discontinue anti-inflammatory and antiplatelet medications (including aspirin and corticosteroids) 1 week prior to and 2 weeks post-procedure.

Bone Marrow Harvesting and Processing

Bone marrow aspiration was performed in an operating room, harvested from the posterior superior iliac spine (PSIS) under strict sterile conditions and fluoroscopic guidance (Fig. 2).

Procedures were conducted under intravenous sedation and local infiltration of 1% lidocaine. The skin was anesthetized with 2 mL of lidocaine using a 25-gauge, 1.5-inch needle, and the periosteum with 5 mL using a 22-gauge, 3.5-inch spinal needle.

All components of the bone marrow aspiration system (Jamshidi needle, trocar, syringes) were pre-flushed with 1 mL of acid citrate dextrose solution A to prevent

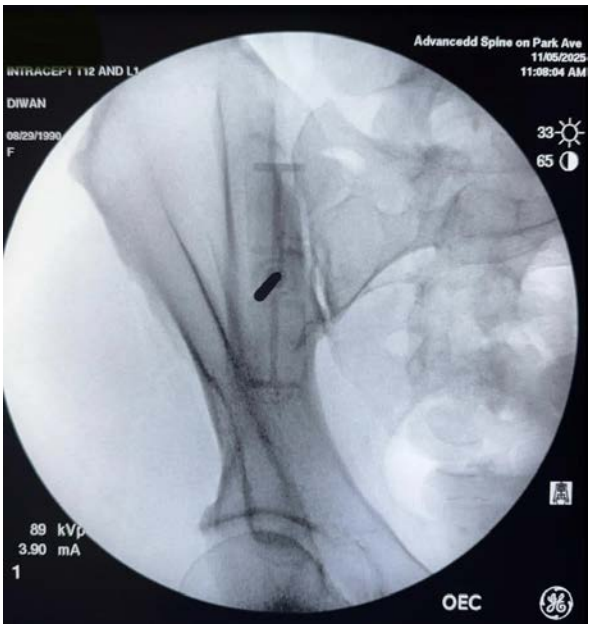

Fig. 2. Anteroposterior fluoroscopic image of bone marrow aspiration performed from the posterior superior iliac spine (PSIS) under sterile conditions and fluoroscopic guidance.

coagulation. The 11-gauge, 11-cm Jamshidi needle was advanced into the subcortical region of the PSIS under coaxial fluoroscopic visualization.

To optimize MSC yield and minimize peripheral blood dilution, small aliquots of 5–10 mL were aspirated using 10 mL syringes under high negative pressure, yielding 50–60 mL of bone marrow in total.

The aspirate was processed immediately in a closed centrifugation system using APEX Biologics, Drucker Boost 4+ Flex, DRK CNTFG-01 at 4,000 rpm for 12 minutes, producing 5-6 mL of BMAC (Fig. 3).

The final product, obtained from the buffy coat layer, was rich with MSCs, hematopoietic stem cells, A2M, platelets, cytokines, and growth factors. Autologous plasma was added to achieve the desired volume. All injections were performed within 30 minutes of preparation. To preserve cell viability, no anesthetics or antibiotics were added to the injectate.

Antibiotic Prophylaxis

All procedures were performed in the operating room, under strict sterile conditions using intermittent biplanar fluoroscopic guidance, and using a needle-in-needle technique (Fig. 4) to enhance precision and minimize tissue trauma and infection.

Each patient received dual intravenous antibiotic prophylaxis with cefazolin (1 g) and gentamicin (80 mg) prior to injection. No intradiscal antibiotics were administered.

Radiofrequency Ablation of the Basivertebral Nerve

Four of the 13 patients received radiofrequency ablation (RFA) of the basivertebral nerve (BVN) prior to the subchondral injections of the BMAC-MSCs. MRI findings in all these patients demonstrated multilevel Modic type 1 or type 2 changes involving the CEPs, consistent with a vertebrogenic pain phenotype. Vertebrogenic pain was diagnosed based on a combination of clinical presentation and imaging findings, including chronic axial low back pain, pain exacerbated by sitting, forward flexion, or transition from sitting to standing, and the presence of Modic type 1 or type 2 endplate changes on MRI, after exclusion of other predominant pain generators such as facet-mediated pain, sacroiliac joint dysfunction, or a compressive radiculopathy.

The corresponding ipsilateral pedicle was entered at the 2 o'clock position on right and the 10 o'clock position on left under fluoroscopic guidance. The skin entry point was infiltrated with 2 mL of 1% lidocaine using a 25-gauge, 1.5-inch needle. A 22-gauge, 3.5-inch spinal needle was used to anesthetize the needle track to the pedicle periosteum. The 8-gauge cannula with diamond tip was then introduced, and using a mallet, the trocar was then advanced through the pedicle to the posterior aspect of the vertebral body.

The trocar was then removed from the cannula and the curved cannula assembly with the J-stylet was inserted. The tip of the J-stylet was placed at the junction of posterior and middle third in the lateral view, and midway between the superior and inferior endplates crossing the midline in the anteroposterior view. The stylet was then removed. The Intracept bipolar radiofrequency probe (Boston Scientific) was connected to the Relievant Medsystems Radiofrequency generator (Fig. 5) and inserted into the introducer cannula. The BVN was then ablated at 85°C for 7 minutes using Relievant's standard radiofrequency algorithm (Figs. 6-8).

Injection Technique

Injectate volumes were standardized as follows:

- Intradiscal: 2–2.5 mL
- Peridiscal: 1 mL
- Subchondral (superior and inferior endplates): 2.5 mL each

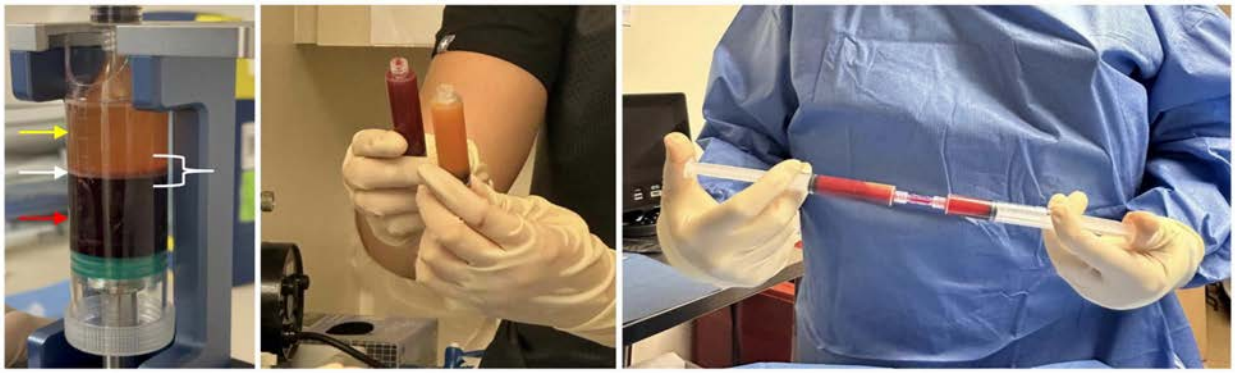

Fig. 3. Bone marrow harvesting and processing for preparation of BMAC. (a) BMAC after centrifugation with buffy coat (white arrow), plasma (yellow arrow), red blood cells (red arrow) and BMAC (white bracket). (b) BMAC and autologous plasma. (c) Mixing the BMAC with the autologous plasma. Images obtained from the authors' own clinical practice.

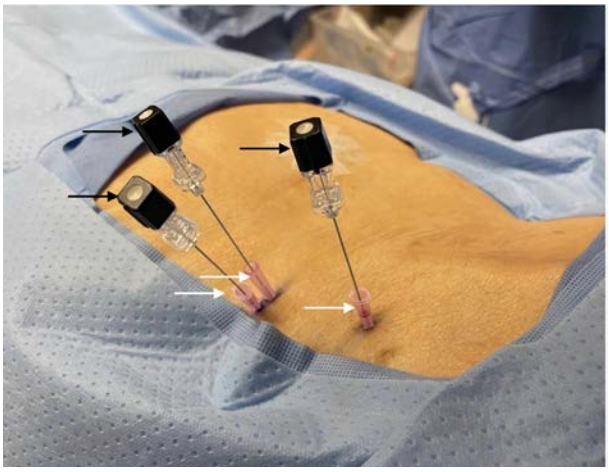

Fig. 4. Needle-in-needle technique. 22-gauge needles (black arrows) are placed through 18-gauge introducer needles to facilitate skin penetration and to reduce the possibility of infection.

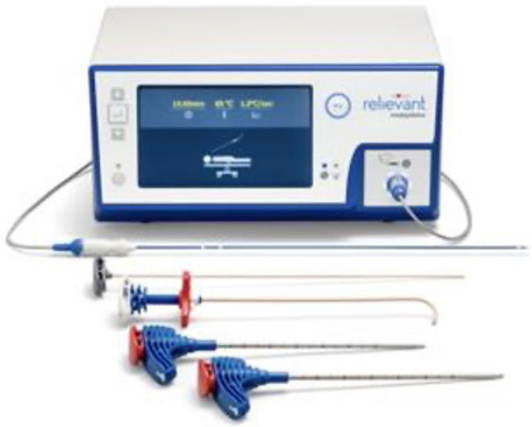

Fig. 5. Relievant Medsystems Radiofrequency generator

Intradiscal Injection

The intradiscal injection followed the procedural principles of diagnostic discography (Fig. 9). A 22-gauge curved-tip needle (6- to 8-inch) was advanced into the center of the nucleus pulposus under fluoroscopic guidance in both anteroposterior and lateral projections.

After confirming needle placement, 2–2.5 mL of freshly prepared BMAC-MSCs was injected slowly to avoid excessive intradiscal pressure and prevent annular leakage. The selected injectate volume was based on previously published intradiscal BMC protocols, which have used approximately 2 mL per treated disc (9).

This step allowed for accurate delivery of regenerative cells and growth factors into the disc while minimizing structural trauma.

Peridiscal Injection (Fig. 7B(e))

Immediately following intradiscal injection, the needle was partially withdrawn under real-time fluoroscopy until its tip was positioned just outside the annulus fibrosus. Approximately 1 mL of BMAC-MSCs was injected into the peridiscal space, targeting the outer annular and perineural regions. This approach has been proposed for symptomatic relief by modulating local inflammatory and nociceptive processes, and for annular tear healing through paracrine mechanisms, as suggested by prior preclinical and clinical studies (9,12-14).

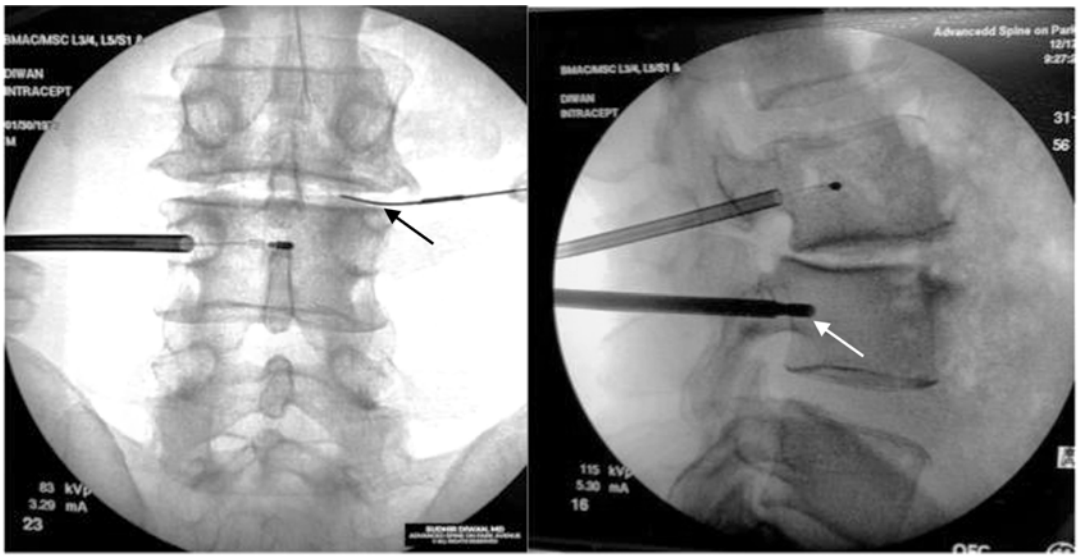

Fig. 6. Basivertebral nerve radiofrequency ablation (BVN-RFA) performed under fluoroscopic guidance. The left image (a) shows an anteroposterior (AP) fluoroscopic view with the intradiscal needle in position (black arrow), while the right image (b) demonstrates a lateral fluoroscopic view confirming appropriate cannula placement for BVN-RFA within the vertebral body (white arrow).

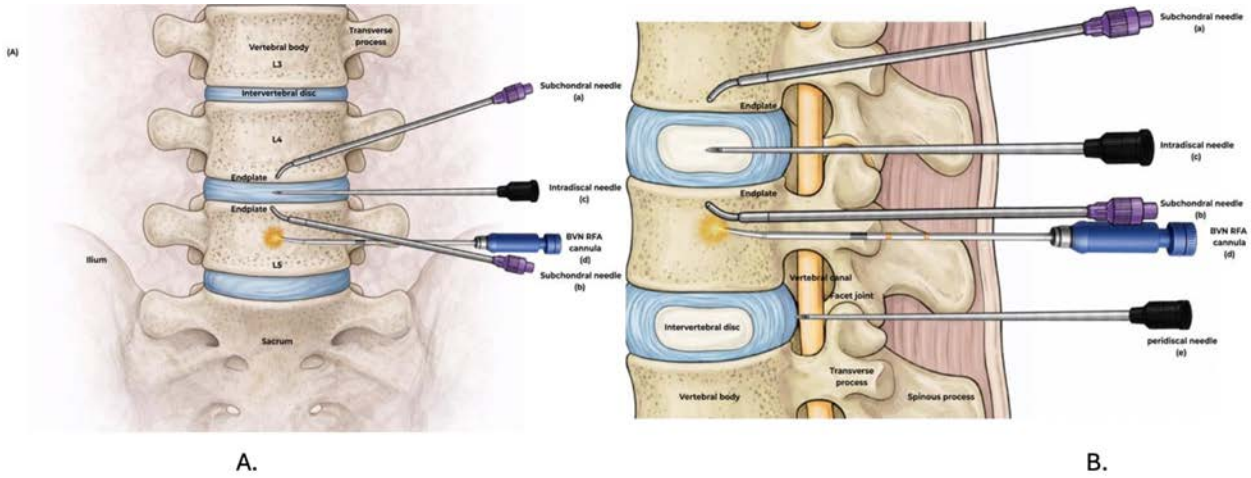

Fig. 7. Anteroposterior (AP) (a) and lateral (b) diagrammatic representation views illustrate the combined regenerative injection strategy targeting the intervertebral disc, cartilaginous endplates and periphery of the disc, and adjacent vertebral subchondral bone.

In the AP view (A), an intradiscal needle (c) is positioned centrally within the nucleus pulposus while curved subchondral needles (a, b) are advanced via a transpedicular approach toward the superior (a) and inferior (b) vertebral endplates. A basivertebral nerve radiofrequency ablation (BVN-RFA) cannula (d) is shown reaching the junction of posterior and middle 1/3 of the vertebral body for RFA of BVN. This is performed as an adjunctive step prior to BMAC-MSCs biologic delivery. The lateral view (B) demonstrates the spatial relationship between intradiscal (c), peridiscal (e) and subchondral (a,b) targets for injecting the BMAC-MSCs and the BVN-RFA cannula (d), highlighting precise needle placements relative to the pedicle, spinal canal, endplates, and intervertebral disc.

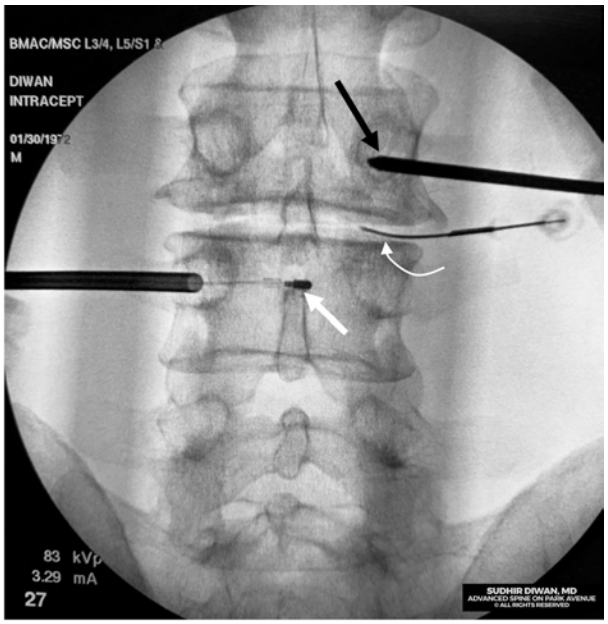

Fig. 8. Anteroposterior fluoroscopic view demonstrating a combined procedure including basivertebral nerve radiofrequency ablation probe (BVN-RFA) (white arrow), transpedicular access needle (black arrow), and intradiscal injection at the same lumbar level (curved white arrow). A transpedicular cannula is positioned within the vertebral body (black arrow) consistent with BVN-RFA targeting along with access for coaxial needle placement for subchondral delivery adjacent to the cartilaginous endplate. The separate smaller spinal needle (white curved arrow) confirms intradiscal access under fluoroscopic guidance.

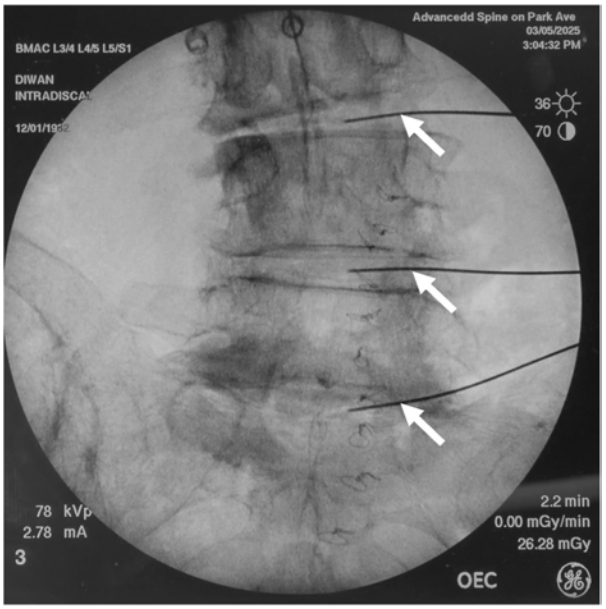

Fig. 9. Anteroposterior fluoroscopic view demonstrating multilevel lumbar intradiscal injection with 22 gauge needles (white arrows).

Combined intradiscal, peridiscal, and subchondral delivery provides a multifocal regenerative approach, addressing both structural and biochemical mechanisms of chronic discogenic and vertebrogenic pain.

Subchondral Injection Approaches

Transpedicular Approach

Subchondral injections were performed by using a transpedicular approach, similar to the trajectory used for RFA of the BVN (Fig. 10). A Jamshidi trocar–cannula system was advanced under anteroposterior, oblique, and lateral fluoroscopic guidance to reach the vertebral body adjacent to the affected endplate.

Trajectory planning (Fig. 11): The clock-face orientation was used to facilitate reproducible transpedicular access to the subchondral region adjacent to the superior and inferior cartilaginous endplates while avoiding violation of the spinal canal.

-→Inferior endplate: right pedicle, 2 o'clock → 8 o'clock trajectory; left pedicle, 10 o'clock → 4 o'clock trajectory.

-→Superior endplate: right pedicle, 4 o'clock → 10 o'clock trajectory; left pedicle, 8 o'clock → 2 o'clock trajectory. Once the Jamshidi trocar reached the subcortical region, the stylet was removed and a curved 8-inch, 16- to 18-gauge spinal needle was introduced coaxially.

Approximately 2.5 mL of BMAC-MSC was injected into the subchondral area adjacent to each corresponding superior and inferior CEPs, ensuring smooth, low-pressure delivery for uniform distribution close to the endplates. In select cases, intraosseous RFA of BVN was performed prior to biologic injection, aiming to reduce nociceptive signaling.

Transdiscal Approach

When feasible, a transdiscal approach was employed, allowing sequential subchondral, intradiscal, and peridiscal injections through a single access point using an 18- to 20-gauge curved-tip needle technique (Fig. 12). This method minimizes radiation exposure and procedural time. Calcified or sclerotic endplates can pose technical challenges, occasionally requiring modi-

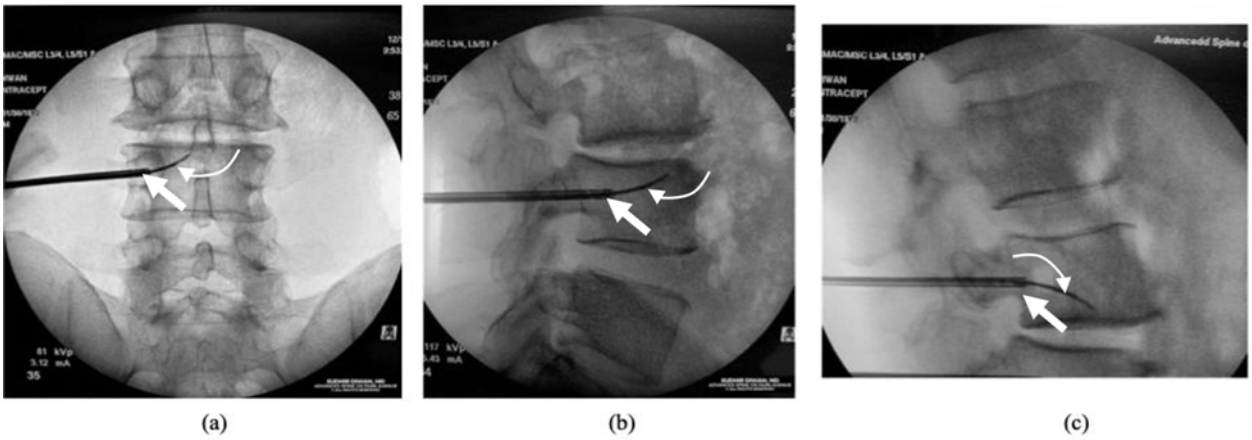

Fig. 10. Anteroposterior (a) and lateral fluoroscopic views (b and c) demonstrating transpedicular access for subchondral injection targeting superior (a and b) and inferior (c) endplates. The cannula (white arrow) and coaxial subchondral needle (curved white arrow) are positioned within the vertebral body, confirming appropriate trajectory and depth for targeted delivery adjacent to the vertebral endplate under fluoroscopic guidance.

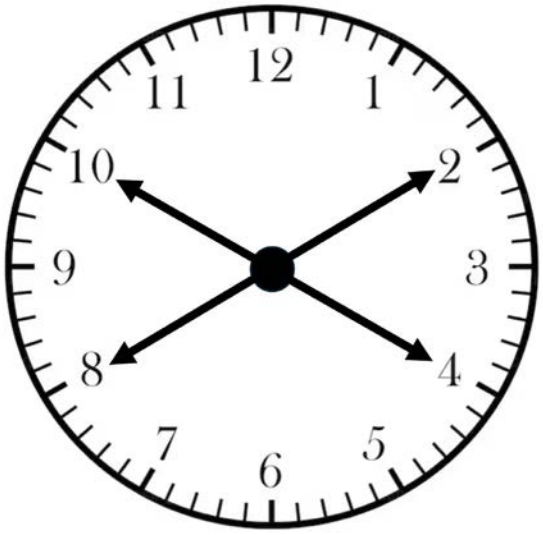

Fig. 11. Schematic representation of the clock-face orientation used to guide needle trajectory during transpedicular subchondral access to the vertebral endplates.

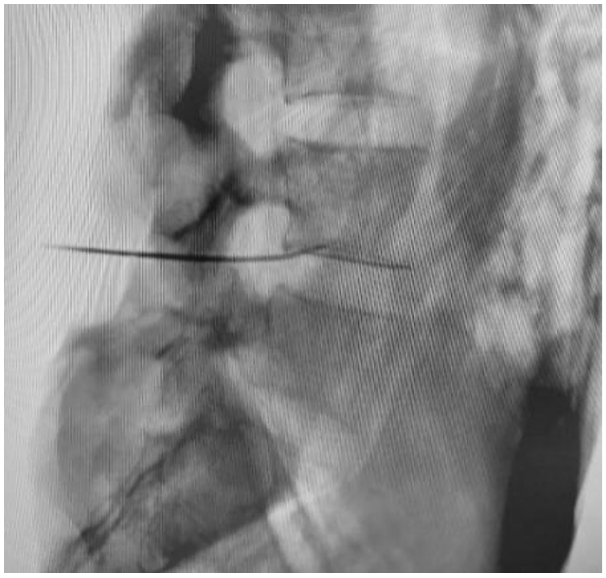

Fig. 12. Lateral fluoroscopic view demonstrating a transdiscal approach for subchondral injection targeting the inferior vertebral endplate.

fied angulation or alternative trajectories to achieve adequate subchondral penetration.

Data Collection

Baseline demographics, MRI findings, pre-treatment VAS pain scores, functional status, and patient satisfaction were recorded prior to the procedure.

Post-procedure follow-ups were performed at 2 weeks, 1 month, and during subsequent clinical visits up to 15 months, documenting VAS, functional capacity, and patient-reported satisfaction.

Statistical Analysis

Continuous variables were summarized using means and standard deviations (SDs). For each patient, the absolute change in VAS score was calculated by subtract-

ing the post-treatment score from the baseline score. Percentage pain reduction was calculated as [(baseline VAS – post-treatment VAS) / baseline VAS] × 100. The mean absolute change and mean percentage reduction were then calculated across the 13 paired observations. The standardized within patient effect size was calculated as Cohen's d by dividing the mean VAS change by the SD of the individual change scores. No inferential hypothesis testing was performed.

RESULTS

A total of 13 patients met inclusion criteria and underwent combined intradiscal, peridiscal, and subchondral injections of BMAC-MSCs mixed with autologous plasma to achieve the volume required for the treatment of chronic vertebrogenic and/or discogenic low back pain. Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

The cohort included 13 patients (6 men and 7 women), with a mean age of 56.2 ± 17.5 years (range, 27–82 years). All patients demonstrated MRI evidence of degenerative disc disease with associated Modic type 1 or type 2 endplate changes. Coexisting lumbar pathologies included spondylolysis, spondylosis, disc bulges and protrusions causing radiculopathy and contributing to chronic axial low back pain. The group also included patients who had undergone prior unsuccessful spinal interventions, reflecting the heterogeneity typically seen in populations with refractory vertebrogenic and discogenic axial chronic low back pain.

Four patients (30.8%) had undergone basivertebral nerve radiofrequency ablation (BVN-RFA) before receiving the biologic intervention. The remaining 9 patients were treated with combined intradiscal, peridiscal, and subchondral BMAC-MSC injections without prior BVN-RFA.

Clinical outcomes and patient-reported results following treatment are summarized in Tables 2 and 3 and Fig. 13.

Baseline mean VAS pain score was 7.3 ± 2.0, decreasing to 2.1 ± 1.6 at the most recent follow-up (4–15 months), corresponding to a mean absolute reduction of 5.2 ± 1.8 points. The mean percentage pain reduction across the cohort was 72.7% ± 19.5%.

The standardized within-patient eaect size was large, with a paired Cohen's d of 2.85. This value was calculated by dividing the mean within-patient reduction in VAS score (5.23 points) by the SD of the individual change scores (1.83 points).

Five patients (38.5%) achieved marked or near-complete pain relief (≥80% reduction), 5 (38.5%) experienced substantial improvement (60–79% reduction), and 3 (23.1%) demonstrated moderate but clinically meaningful improvement (50–59% reduction). Importantly, all patients achieved at least a 50% reduction in pain intensity, and no nonresponsive patients were identified.

Patient-reported outcomes consistently demonstrated functional improvement, including enhanced mobility, increased walking tolerance, improved sleep quality,

Table 1. Baseline demographic and clinical characteristics of the study population (n = 13).

Patient ID	Age (years)	Sex	Primary diagnosis*
DAJ0000005	68	M	Vertebrogenic LBP; lumbar spondylolysis; lumbar disc disorders
SHMA000006	66	F	Vertebrogenic LBP; disc degeneration; lumbar spondylosis
BEST000002	82	M	Vertebrogenic LBP; disc degeneration
PER0000011	72	M	Lumbar disc degeneration; lumbar spondylolysis
OCFR000001	48	M	Vertebrogenic LBP; lumbar disc degeneration
RACA000002	77	F	Vertebrogenic LBP; lumbar spondylosis; disc disorders
KAJA07AF448A	27	M	Vertebrogenic LBP; lumbar spondylolysis; disc degeneration
MASH07BEEC94	66	F	Vertebrogenic LBP; disc degeneration; post-laminectomy syndrome
ARJE000001	35	F	Vertebrogenic LBP; thoracolumbar disc degeneration
DEAL07C47AED	45	F	Vertebrogenic LBP; lumbar spondylosis; disc disorders
MAEM07CA4B06	53	M	Vertebrogenic LBP; lumbar spondylolysis; disc disorders
P1_SLO	35	M	Lumbar disc disorders with radiculopathy
P2_SLO	53	F	Lumbar disc disorders with radiculopathy

Abbreviations: VAS, Visual Analog Scale; BVN-RFA, basivertebral nerve radiofrequency ablation.

and return to exercise. Patient satisfaction was high: 38.5% reported being very satisfied, 53.8% satisfied, and 7.7% neutral. All patients (100%) indicated they would recommend the procedure to friends and family members.

Satisfaction

Patient satisfaction was assessed using a 4-point ordinal scale (very satisfied, satisfied, neutral, or unsatisfied). Descriptive analyses were performed to summarize satisfaction outcomes at follow-up. Most patients reported being either very satisfied or satisfied with the procedure, and all patients indicated that they would recommend the treatment. Even the patient who experienced only partial clinical improvement described the intervention as beneficial compared to prior therapies.

ADVERSE EVENTS

No major procedure-related complications were observed. Two patients reported mild post-injection soreness at the PSIS harvest site, which resolved spontaneously within 48 hours without the need for intervention. Some patients reported mild diffuse muscle spasms due to multiple injection sites, but none required any treatments other than ice application. There were no cases of infection, bleeding, neurological deficit, discitis, or other serious adverse events during the follow-up period.

Imaging and Follow-up

Routine post-procedural MRI was not uniformly obtained across the cohort. However, at the latest clinical follow-up, the patients demonstrated sustained symptomatic and functional improvement. We also observed that improvements at the latest follow-up

Table 2. Pain intensity before and after combined intradiscal, peridiscal, and subchondral BMAC-MSC treatment (n = 13).

Patient ID	Baseline VAS	Post-treatment VAS	Absolute reduction	Percent reduction
DAJ0000005	3	0	3	100%
SHMA000006	10	4	6	60%
BEST000002	7	0	7	100%
PER0000011	9	1	8	88.9%
OCFR000001	8	0	8	100%
RACA000002	10	5	5	50%
KAJA07AF448A	6	2	4	66.7%
MASH07BEEC94	8	3	5	62.5%
ARJE000001	8	1	7	87.5%
DEAL07C47AED	5	2	3	60%
MAEM07CA4B06	8	3	5	62.5%
P1_SLO	6	3	3	50%
P2_SLO	7	3	4	57.1%

Abbreviations: VAS, Visual Analog Scale.

Table 3. Clinical outcomes and patient-reported results following treatment.

Patient ID	Follow-up duration (months)	BVN-RFA	Functional improvement*	Patient satisfaction	Would recommend
DAJ0000005	8	No	Major improvement	Very satisfied	Yes
SHMA000006	12	Yes	Significant improvement	Satisfied	Yes
BEST000002	12	No	Major improvement	Very satisfied	Yes
PER0000011	14	Yes	Major improvement	Very satisfied	Yes
OCFR000001	15	No	Major improvement	Very satisfied	Yes
RACA000002	10	No	Significant improvement	Satisfied	Yes
KAJA07AF448A	8	No	Significant improvement	Satisfied	Yes
MASH07BEEC94	6	No	Near-complete pain relief	Satisfied	Yes
ARJE000001	5	Yes	Significant improvement	Very satisfied	Yes
DEAL07C47AED	8	No	Significant improvement	Satisfied	Yes
MAEM07CA4B06	4	Yes	Significant improvement	Satisfied	Yes
P1_SLO	9	No	Moderate improvement	Neutral	Yes
P2_SLO	6	No	Moderate improvement	Satisfied	Yes

*Functional improvement assessed based on patient-reported changes in mobility, daily activities, sleep, and quality of life.
Abbreviations: BVN-RFA, basivertebral nerve radiofrequency ablation; ROM, range of motion; QoL, quality of lif

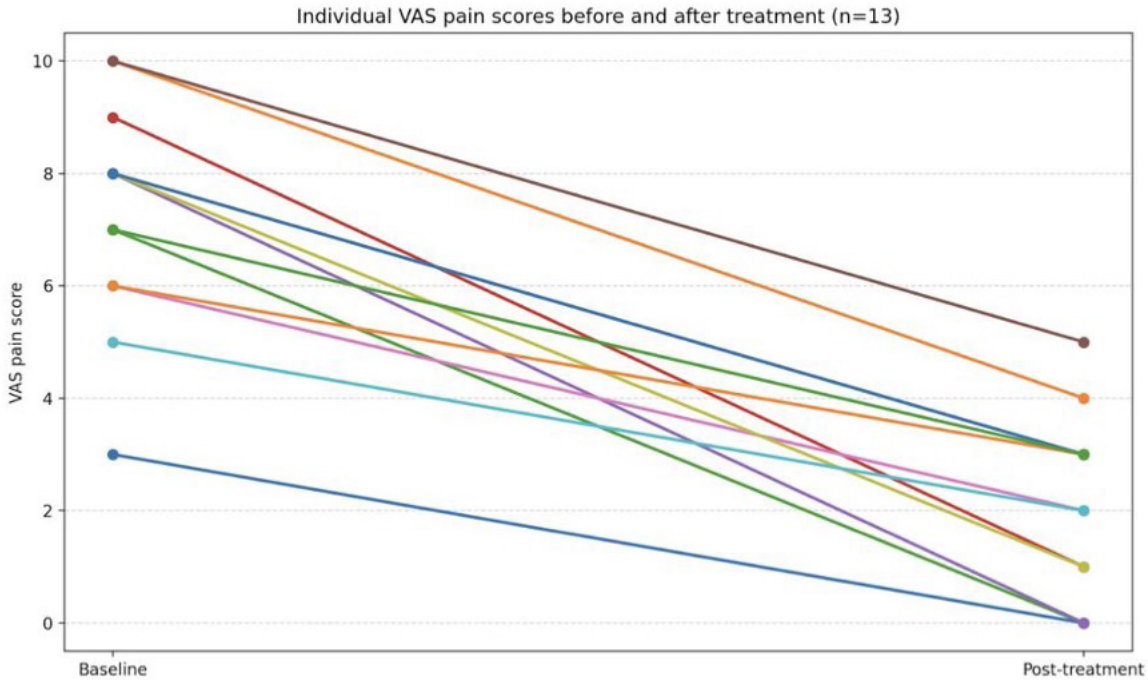

Fig. 13. Individual pain scores before and after treatment. Each line represents an individual patient, connecting baseline and post-treatment Visual Analog Scale (VAS) pain scores following combined intradiscal, peridiscal and subchondral biologic injections.

were better compared to earlier follow-ups. Patients who underwent concurrent basivertebral nerve radiofrequency ablation (BVN-RFA) appeared to experience earlier subjective pain relief, but the small sample size precluded formal subgroup comparisons. Favorable outcomes were observed in both BVN-RFA and non-BVN-RFA groups.

Across the study population, most patients with available paired data demonstrated a meaningful reduction in pain intensity following treatment. Improvements were observed despite heterogeneity in baseline diagnoses and follow-up duration. Several patients reported substantial functional gains, including improved mobility, sleep quality, and ability to resume physical activity.

DISCUSSION

The results of the present study demonstrated that in a retrospective case series of 13 patients with refractory vertebrogenic and discogenic low back pain, with multilevel Modic type 1 and 2 changes, with or without lumbar radiculopathy treated with combined intradiscal, peridiscal, and subchondral BMAC-MSC injections, there were clinically meaningful improvements in pain and function without any major complications. Most patients experienced marked pain reduction and sustained functional recovery over several months, with continued improvement. These findings support the potential clinical value of a multifocal biologic strategy targeting the disc–endplate–subchondral bone unit in degenerative spine disease. Ongoing follow-up will allow further characterization of outcome durability and longer-term clinical trajectories.

Biological Rationale and Mechanisms

Regenerative medicine in spine care goes beyond palliative measures and introduces an active biological strategy designed to modify the course of disease. Traditional approaches, such as analgesics, physical therapy, or minimally invasive procedures, tend to provide only symptomatic relief without addressing underlying pathology. Regenerative therapies, on the other hand, target structural and biochemical processes simultaneously.

The initial expected benefit is symptomatic relief, achieved by modulating inflammatory activity in the amphiarthrodial joint or disc, dampening nociceptive pathways, and improving pain scores early in the treatment course. Beyond this, these therapies aim to heal tissue injury itself. In the spine, this includes promoting repair of microfractures of the CEPs and subchondral bone, sealing annular fissures, restoring endplate integrity, and possibly restoring nutrient diffusion and improved biomechanics.

A second goal is to stop or slow the progression of degeneration. Once endplate and subchondral structures are compromised, a self-perpetuating cycle of mechanical stress, inflammation, and apoptosis drives disc degeneration (4). Delivering MSCs and growth factors directly to these structures may interrupt this cycle.

Finally, regenerative medicine aspires to regenerate tissue rather than merely stabilize it. Experimental data suggest that MSCs can differentiate into chondrocyte-like cells, synthesize extracellular matrix, and stimulate angiogenesis in the subchondral region (4).

Importance of Targeting Subchondral Bone to Prevent Segmental Instability

Degenerated intervertebral discs and CEPs associated with Modic changes 1 and 2 are characterized by pathological alterations of the vertebral endplates and adjacent subchondral bone, including inflammatory bone marrow changes and structural endplate damage (3). Experimental and clinical studies have demonstrated that disruption of the cartilaginous endplate facilitates biochemical communication between the intervertebral disc and vertebral body, allowing inflammatory mediators to cross the bone–disc interface and contributing to pain generation and further progression of disc degeneration (3,6,7).

Targeting the subchondral bone through biologic interventions such as subchondral delivery of MSC-rich BMAC is therefore biologically plausible. MSCs have been shown to exert immunomodulatory and anti-inflammatory effects within subchondral bone, including regulation of bone remodeling and suppression of inflammatory activity, which are central mechanisms implicated in degenerative musculoskeletal conditions (15). In the context of the spine, restoration of the subchondral bone and endplate microenvironment may support the structural and metabolic function of the disc–endplate complex, limiting segmental instability and improving the nutrition of the disc.

In addition, intradiscal delivery of BMAC has been associated with clinical improvement in patients with discogenic low back pain, supporting the concept that biologic modulation of the disc and its adjacent structures can influence symptoms and function (9). Integrative models of spinal degeneration further emphasize the role of endplate and subchondral bone pathology as contributors to disc degeneration and pain, reinforcing the rationale for therapies that directly target these compartments (4).

Degeneration and Molecular Cascades

Degeneration begins with subtle microstructural damage that accumulates over time, eventually causing both structural failure and chronic symptoms. This process is influenced by intrinsic factors, such as age-related cell senescence, genetic predisposition, and reduced regenerative capacity, and extrinsic factors, such as repetitive microtrauma, poor posture, smoking, obesity, and chronic low-grade inflammation (2,3).

Microscopically, degeneration involves loss of matrix proteins, reduced disc hydration, and endplate microdamage, which impair nutrient diffusion and waste clearance. Progression leads to annular fissures, bulging, or herniation. The adjacent subchondral bone responds with sclerosis, osteophyte formation, and Modic changes, which are markers of inflammation and altered bone turnover (16,17). This cascade alters biomechanics, disrupts load distribution, and perpetuates inflammation through cytokines and neuropeptides thus creating the chronic pain phenotype.

At the molecular level, mechanical stress activates inflammatory pathways, increasing tumor necrosis factor-alpha, interleukins (IL-1β, IL-6), and matrix metalloproteinases. These factors degrade collagen and proteoglycans, while oxidative stress and mitochondrial dysfunction accelerate cell death. BMAC-derived MSCs can counter these pathways by secreting anti-inflammatory cytokines, promoting angiogenesis, and stimulating progenitor cells, shifting the environment from catabolic to anabolic (4).

Triad of Degeneration

Degeneration is driven by a triad of genetic predisposition, repetitive microtrauma, and compromised nutrition. Genetic susceptibility shapes cellular responses to stress, while microtrauma, whether from repetitive strain or high-impact activities, cause cumulative damage. Nutrition, reliant on endplate vascularity and diffusion, becomes impaired as sclerosis and Modic changes progress (16,17). This triad helps explain why

many patients fail to improve with symptomatic therapies alone. Regenerative strategies aim to modify this biological environment, enhancing healing capacity despite these intrinsic and extrinsic stressors.

Functional Spine Unit as a Complex Biological System

The Functional Spine Unit is the smallest anatomical and biomechanical unit of the spine and consists of two adjacent vertebral bodies, the intervertebral disc, paired facet joints, and supporting ligamentous structures. Rather than functioning as independent components, these structures operate as an integrated motion segment in which mechanical forces, structural integrity, and biological signaling are closely interdependent (18).

The spinal motion segment is an integrated biological system composed of nucleus pulposus, CEPs and vertebral subchondral bone. These components communicate continuously. The discs are avascular structures and receive nutrients by diffusion through the CEP, and subchondral bone provides support and biochemical signaling and nourishes the CEPs. In degeneration of the CEP with Modic 1 and 2 changes, structural damage of one component affects others. For example, disc degeneration with narrow disc space can lead to abnormal load transfer and subchondral sclerosis (15). In the spine, endplate damage similarly compromises disc nutrition and triggers degenerative cascades. Regenerative approaches take this interdependence into account, targeting both cartilage and subchondral structures to restore structural homeostasis.

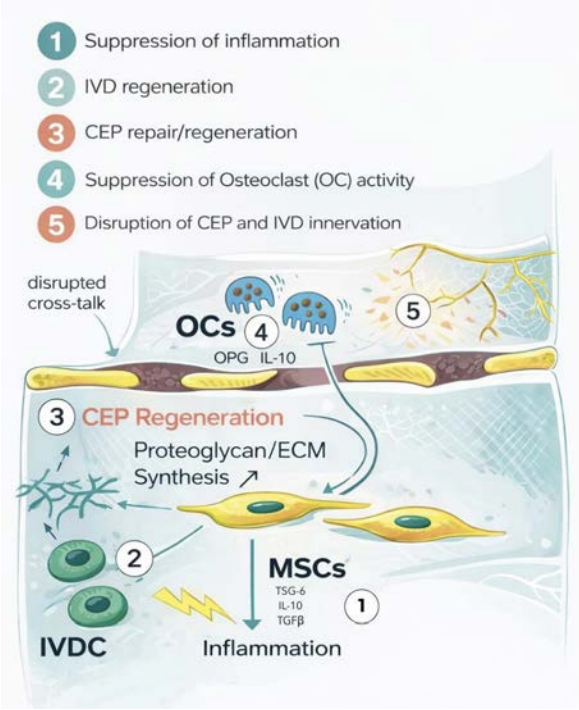

Fig. 14. Schematic illustration of the proposed multimodal mechanisms of action of intradiscally injected MSCs in Modic type 1 changes. MSCs may contribute to disc repair and sealing of CEP defects, potentially improving tolerance to mechanical loading. Suppression of disc inflammation and sealing of CEP defects may also disrupt inflammatory crosstalk between the disc and bone marrow. Adapted and modified from Herger et al (4).
Abbreviations: IVDC, intervertebral disc complex; OCs, osteoclasts; MSCs, mesenchymal stem cells; ECM, extracellular matrix.

Targeting Subchondral Bone for Repair and Regeneration

Emerging evidence highlights the subchondral bone as a key therapeutic target. MSCs in subchondral bone are a novel approach for cartilage regeneration. Tissue adaptation and repair responses are evident in subchondral tissues. In osteoarthritis, osteoclasts release TGF-B from the bone matrix, which modulates MSC activity for bone remodeling activity in subchondral bone (18).

Delivering biologics into the subchondral region can stimulate intrinsic repair mechanisms (15). In the spine, targeting the cartilaginous endplate (CEP) and adjacent subchondral bone may promote healing of endplate microfractures, reduce inflammatory crosstalk between bone and disc, and restore structural integrity of the disc–endplate complex (4).

Fractured and calcified endplates contribute to segmental instability and impaired nutrient diffusion, accelerating disc degeneration. Mesenchymal stem cells (MSCs), with their well-established immunomodulatory and anti-inflammatory properties, may suppress osteoclastic activity, regulate inflammatory signaling, and enhance proteoglycan and extracellular matrix synthesis (4) (Fig. 14).

By facilitating CEP regeneration and improving disc nutrition, subchondral delivery of biologics may not only alleviate inflammation but may also interrupt the degenerative cascade and promote intervertebral disc repair.

Combined Approaches and Literature Support

Studies of knee and hip osteoarthritis suggest that

combined intra-articular and intraosseous injections provide superior outcomes to intra-articular injections alone (10,11). These approaches reach multiple tissues involved in degeneration, including cartilage, synovium, and subchondral bone. Our approach mirrors this principle by combining intradiscal, peridiscal, and subchondral injections, targeting both disc and endplate pathology. This dual strategy may contribute to the significant improvements observed in our series.

Although spine-specific literature remains limited, emerging clinical studies support the concept that biologic therapies may improve and expedite outcomes in patients with Modic 1 and 2 changes associated with chronic low back pain. A prospective pilot study demonstrated significant clinical improvement following intradiscal platelet-rich plasma administration in patients with Modic type 1 changes (17). A prospective study comparing intradiscal versus posterior chain BMAC injections demonstrated greater benefit in discogenic pain (9). Case reports also describe pain and imaging improvements, including regression of Modic 1 and 2 endplate changes and Schmorl's nodes, following combined intradiscal and subchondral therapies (4).

Limitations

This study has inherent limitations. The small sample size (n = 13) and retrospective design limit statistical generalization, as does a lack of a comparator group. This lack of a control or placebo group resulted in an inability to account for natural variation or placebo response.

Heterogeneity in disease stage, prior BVN-RFA, and variable followup intervals introduce potential confounding factors. Previous literature has reported clinical improvement through 12 months following intradiscal BMAC treatment (9); however, morphological improvement was not assessed. In the present study, follow-up imaging was not systematically performed, which prevented objective assessment of structural regeneration or changes in Modic findings.

Despite these constraints, the consistent and clinically meaningful improvements observed across patients support the feasibility and potential efficacy of this multimodal biologic approach.

Future Directions

Future research should prioritize well-designed prospective randomized blinded controlled trials with standardized protocols for BMAC-MSCs preparation, dosage, and biologic delivery target sites. Advanced imaging modalities, particularly MRI with quantitative analysis of endplate integrity and Modic changes, should be integrated to correlate clinical outcomes with structural remodeling (4,19).

Standardization is also required for procedural parameters, including optimization of injectate concentration, delivery targets, and the potential integration of adjunctive therapies such as radiofrequency ablation. Longitudinal MRI follow-up will be essential to document the progression or regression of Modic changes and to evaluate the degree of endplate repair over time (17).

Finally, future investigations should establish robust patient-selection criteria, given the current evidence that individuals with discogenic pain and Modic type 1 changes are the most likely to benefit from regenerative biologic interventions (9).

CONCLUSION

This retrospective case series suggests that combined subchondral, peridiscal, and intradiscal injections of BMAC-derived MSCs may be a safe and clinically beneficial option for selected patients with refractory vertebrogenic pain and degenerative spine disease to avoid surgery.

The observed improvements in pain intensity and functional capacity, even in a small and heterogeneous sample, support the biological rationale for targeting both disc and endplate pathology in a single regenerative approach.

While the results are preliminary, they align with emerging evidence of biologics from the musculoskeletal and spine literature. Further prospective, randomized controlled studies with standardized protocols and long-term follow-up will be necessary to validate these findings, identify predictors of response, and refine patient selection criteria for regenerative spine interventions.

Author Contributions

Sudhir Diwan conceptualized the study.
Sudhir Diwan and Robert Rapcan performed the procedures.
Ana Flávia Vieira Leite, Shelby Muñoz and Eva Manik collected and analyzed the data.
Ana Flávia Vieira Leite and Sudhir Diwan drafted the manuscript.

Michael E. Schatman, Alan D. Kaye, Douglas Beall, Annu Navani, and Robert Rapcan contributed to critical revision of the manuscript.

All authors approved the final version of the manuscript. All authors meet the ICMJE criteria for authorship.

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