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CLINICAL SCIENCE

Allogenic bone marrow–derived mesenchymal stromal cell–based therapy for patients with chronic low back pain: a prospective, multicentre, randomised placebo controlled trial (RESPINE study)

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ABSTRACT

Objectives To assess the efficacy of a single intradiscal injection of allogeneic bone marrow mesenchymal stromal cells (BM-MSCs) versus a sham placebo in patients with chronic low back pain (LBP).

Methods Participants were randomised in a prospective, double-blind, controlled study to receive either sham injection or intradiscal injection of 20 million allogeneic BM-MSC, between April 2018 and December 2022. The first co-primary endpoint was the rate of responders defined by improvement of the Visual Analogue Scale (VAS) for pain of at least 20% and 20 mm, or improvement of the Oswestry Disability Index (ODI) of 20% between baseline and month 12. The secondary structural co-primary endpoint was assessed by the disc fluid content measured by quantitative MRI T2, between baseline and month 12. Secondary endpoints included pain VAS, ODI, the Short Form (SF)-36 and the minimal clinically important difference in all timepoints (1, 3, 6, 12 and 24 months). We determined the immune response associated with allogeneic cell injection between baseline and 6 months. Serious adverse events (SAEs) were recorded.

Results 114 patients were randomised (n=58, BM-MSC group; n=56, sham placebo group). At 12 months, the primary outcome was not reached (74% in the BM-MSC group vs 69% in the placebo group; p=0.77). The groups did not differ in all secondary outcomes. No SAE related to the intervention occurred.

Conclusions While our study did not conclusively demonstrate the efficacy of allogeneic BM-MSCs for LBP, the procedure was safe. Long-term outcomes of MSC therapy for LBP are still being studied.

Trial registration number EudraCT 2017-002092-25/ClinicalTrials.gov: NCT03737461.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mesenchymal stromal cells have been shown to reduce disc inflammation and enhance cartilage matrix remodelling.
⇒ Previous clinical trial suggested potential clinical benefit of mesenchymal stromal cell (MSC) intradiscal injection in degenerative disc disease (DDD) but these trials were not conclusive.

WHAT THIS STUDY ADDS

⇒ We conducted a large multicentric randomised placebo-controlled study in DDD using a single intradiscal injection of allogeneic MSCs.
⇒ Our data demonstrate that the procedure is safe. At month 12, we did not demonstrate clinical and imaging benefits as we did not reach our co-primary endpoint.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The RESPINE study provides valuable insights into the complexities of MSC therapy in a challenging clinical context.
⇒ Further research should aim not only to refine MSC therapies but also to explore combinatory approaches that address the multifactorial nature of disc degeneration and chronic pain.

INTRODUCTION

Low back pain (LBP) is the single most common cause for disability in individuals aged 45 years or younger and more than half a billion people are currently suffering worldwide.[1] Chronic LBP limits both quality of life and productivity of patients while increasing the need for access to healthcare.[2] Intervertebral disc degeneration (IDD) is the most significant cause of chronic LBP.[3 4] Current treatment options for LBP due to IDD range from anti-inflammatory drugs to invasive procedures including spine fusion and, more recently, disc

replacement surgery. However, these treatments are symptom-modifying without structural restoration.[5] Recently, there has been a growing interest in developing novel strategies that aim to repair the degenerated disc and restore biological function.[6]

Bone marrow mesenchymal stem/stromal cells (BM-MSC) are skeletal progenitor cells that have the ability to differentiate into various cell types, including bone, cartilage and fat cells.[7] Due to their ability to regenerate damaged tissue and reduce inflammation,[8] BM-MSCs have been investigated as a potential treatment for IDD, a condition characterised by the breakdown of the intervertebral disc (IVD) that cushions the spinal vertebrae.[9 10] MSCs are able to respond to their microenvironment through the secretion of a myriad of biological factors able to modulate immune response, tissue regeneration and repair processes.[11 12] It is commonly acknowledged that these mechanisms may involve the ability of MSC to secrete a large panel of pro-regenerative biological factors directly in the extracellular environment or mediated through the production of extracellular vesicles containing a cargo of growth factors and other molecules capable of stimulating cell proliferation, differentiation and extracellular matrix synthesis. These include members of the transforming growth factor (TGF) superfamily, including TGFbeta and bone morphogenic proteins, hepatocyte growth factor and vascular endothelial growth factor, among others.[13–15] Several in vitro and in vivo studies have been carried out which indicated increased proteoglycan synthesis, reduced levels of proinflammatory cytokines and matrix-degrading enzymes as well as structural benefit (restoration of disc height and imaging scores).[16] However, our understanding of the mechanism(s) of action underpinning the therapeutic effects of MSC in IDD is still incomplete.[6]

Encouraging preliminary results suggested that MSC-based regenerative therapies may provide positive outcomes for this common and debilitating disease. Orozco *et al* conducted a pilot phase I clinical study in patients affected by chronic LBP due to early IDD in a single disc.[17] Patients exhibited rapid and progressive improvement of functional indexes of 65% to 78% over 1 year after intradiscal administration of autologous BM-MSCs. The procedure appeared to be safe and no side effects were reported. The first pilot randomised controlled trial (RCT) to evaluate the efficacy of allogeneic BM-MSC therapy for IDD was conducted by Noriega *et al*.[18] In this phase IIa trial, 24 patients with chronic LBP associated with single level IDD were randomly allocated to BM-MSC intradiscal injection or sham treatment. A significant improvement of pain and functional scores was documented at 3 months and was maintained for at least 1 year in the cell-treated group compared with the control group. In addition, MRI-based IDD scores demonstrated a significant improvement in the treated group. In addition, the Mesoblast trial tested intradiscal administration of allogeneic Stro-1-selected BM-MSCs in a prospective phase II RCT involving 100 patients with chronic, moderate to severe LBP caused by early single level IDD.[19] In this study, patients were randomised to receive one of two different doses of cells and control patients received either saline or hyaluronic acid injection. 69% of the cell-treated groups achieved 50% reduction in pain compared with 31% in the control groups. However, the long-term benefit of the treatment and an assessment of changes in disc water content, a reflection of proteoglycan density, assessed on T2 sequence lumbar MRI, are still lacking.

Here, we report the outcome of a randomised, double-blinded trial in patients with chronic LBP due to single level IDD, persistent for more than 3 months despite conventional medical therapy and without previous surgery. This study evaluated the efficacy of a single intradiscal allogeneic BM-MSC injection versus sham placebo procedure by assessment of pain reduction, functional score and potential change in disc water content after 12 and 24 months.

MATERIALS AND METHODS

Study design

The RESPINE trial was designed as a multicentre randomised, placebo-controlled, double-blind phase IIb trial to compare allogeneic adult BM-MSC therapy and sham-treated controls in subjects with chronic LBP. The clinical trial is registered on EudraCT (number 2017-002092-25) and on clinicaltrials.gov (NCT03737461). All participants provided written informed consent.

Patient selection and enrolment

Participants were recruited by orthopaedic and rheumatology clinicians at six university hospitals in four European countries (France, Spain, Italy and Germany) from April 2018 to April 2021. Patients were selected from a cohort database and by employing print and social media. Eligible participants were aged 18–60 years old, had chronic LBP unresponsive to conservative therapy (including physical therapy and pain medication with level two painkillers[20]) for at least 3 months and had LBP ≥40/100 on a numeric pain rating scale at enrolment. In addition, patients had spine MRI assessment with lumbar IDD grade 4–7 according to the modified Pfirrmann degenerative scale assessed using T2-weighted MRI[21] at one lumbar level from L1 to S1. A second adjacent level of IDD was allowed with a maximum modified Pfirrmann's grade of 4. Use of non-steroidal anti-inflammatory drugs (NSAIDs) was excluded for at least 48 hours and painkillers for 24 hours prior to assessment. The criteria for selection of the disc to receive treatment were defined by the Barcelona centre team considering a sufficient disc space (height loss not below more than 50%), or presence of magnetic remodelling (Modic type I or II changes at the same level of the lumbar disc), and absence of disc herniations (≤3 mm protrusion) with no evidence on imaging of neurological compression. All patients interviewed for eligibility underwent a T2 lumbar MRI in the Radiology Centre at each clinical site. Each T2 mapping MRI was performed using a fast spin echo sequence of the middle sagittal area of the IVD at the time of inclusion and at month 12 and 24 after treatment. The anonymised MRI data were sent to ITRT Barcelona, Spain, by a secure and approved data transfer protocol for analysis. All MRI data were assessed by the same radiologist throughout the trial.

Criteria for exclusion included pregnancy, breastfeeding, congenital or acquired diseases leading to spine deformations (hyperlordosis, scoliosis, isthmus spondylolysis, sacralisation and hemisacralisation), spinal canal stenosis a history of spinal infection, lumbar disc herniation, spinal segmental instability, previous spine surgery or symptomatic posterior lumbo-articular osteoarthritis or predominant facet syndrome on X-ray or MRI (osteophyte and facet hypertrophy), a history of cancer or other malignant condition, an atypical chronic pain syndrome, oral, intramuscular, intravenous or epidural steroid therapy within the previous 3 months prior to treatment injection, a current diagnosis of bleeding disorders and/or taking prescribed anticoagulants that could not be discontinued and an history of allergy to any substances used in the treatments (online supplemental file 1).

Cell production, isolation, expansion and transport

We used allogeneic BM-MSC prepared as described previously.[18 22] Briefly, bone marrow (BM) was aspirated from three healthy volunteers of age 30–50 years, who had consented to the use of their cells for allogeneic patient treatment. BM-MSCs were processed under good manufactoring procedure (GMP) conditions at the Citospin cell production facility (PEI number 15-007) in Valladolid, Spain. Bags containing 100–150 mL of heparinised (BM) were shipped to the facility in a controlled temperature (2–15°C) container, assessed for integrity, weighed and immediately processed in the clean room for isolation and expansion of the cells.

The expansion procedure was performed as previously described.[18 23] Briefly, the mononuclear fraction was isolated by density gradient centrifugation using Ficoll-Paque (GE Healthcare Bio-Sciences, AB, Buckinghamshire, England) and cultured in 175 cm^2 tissue culture flasks (Corning) with cell culture medium consisting of 10% fetal bovine serum, 1% gentamycin in Dulbecco's modified Eagle medium (all from Gibco) and incubated at 37°C under 10% CO_2 until the adherent cells achieved 80% confluence. These cells were characterised by flow cytometry following the most recent update on minimal release criteria for MSC proposed by the International Society for Cell Therapy.[24 25] These criteria refer to positive expression (≥97%) of CD105, CD73, CD90 and CD166 markers and negative expression (≤1%) of CD34 (haematopoietic stem cells and endothelial cells), CD45 (leucocytes and haematopoietic progenitors), CD14 (monocytes and macrophages) and HLA-DR (human leucocyte antigen). These results suggested the presence of MSC and the absence of other cell types in the expanded cell populations. At this point, cells were resuspended in 5% dimethyl sulfoxide or Cryostor CS 5, and were frozen in liquid nitrogen in aliquots of 10 million cells/mL in 2 mL vials until needed. For quality control, these cell stocks were tested on thawing for expression of the same marker panel as well as potency determined in assessing chondrogenic differentiation and cumulative duplications (≤5). Previous data have indicated that cells frozen under these conditions remain stable for at least 5 years.

When a patient was confirmed for inclusion in the cell treatment arm of the study, cells were thawed at room temperature and centrifuged to remove the cryoprotectant. They were then resuspended in fresh culture medium and expanded in culture for 7–10 days as described. Finally, the expanded cell preparations were tested for cell count, viability, mycoplasma, identity, sterility and cumulative duplication. The cell dose was formulated to contain 20 million cells/2 mL of Hypothermosol (Stem Cell Technologies) validated to maintain >85% viability for 72 hours at 2–8°C.[23] The Investigational Medicinal Product Dossier (IMPD) number was elaborated by Citospin and University of Valladolid and was approved by the regulatory authority La Agencia Espanola de Medicamentos y Productos Sanitarios.

Intradiscal injection

On day 0, the treatment administration day, each patient received a 2 mL intradiscal injection of 20 million BM-MSCs in injectable-grade Plasma-Lyte using a 22G spinal needle. This dose was selected based on previous clinical and preclinical studies.[17 26] Under sterile conditions, with the patient in prone position under mild sedation, the intradiscal injection into the symptomatic disc was performed using a right postero-lateral approach under live C-arm fluoroscopy. All injections were performed by the same physician in each hospital to ensure standardisation of technique.

Injection and post-procedure care (anaesthesia and analgesia) were performed in accordance with standard of care as appropriate in the judgement of the treating physician. The injection was performed in the surgical theatre with a recommendation for 24 hours of home rest without specific restriction of activity. All participants were seen 1 week post-injection to check for infection and to evaluate the extent of any post-procedure pain flares. The sham injection without intradiscal puncture consisted on subcutaneous injection in the back of the patient of 2 mL of sterile saline in similar conditions in the surgical theatre.

Randomisation and blinding

Patients were randomly assigned to allogeneic BM-MSC or placebo in a 1:1 allocation using a centralised randomisation system with Ennov software (Clinsight) under the responsibilities of Montpellier University hospital (CHUM). Randomisation was stratified by centre. After BM-MSC therapy, participants attended the clinic and were contacted by telephone to complete the primary safety and efficacy outcome measures at 1, 3, 6, 9, 12 and 24 months post-treatment. The physician in charge of follow-up was different from the surgeon/radiologist who performed the treatment. All participants, assessors, the biostatistician and the physician in charge of follow-up were blinded to the assigned treatment. The surgeon/radiologist who performed the injection was not blinded to the randomisation assignment and did not have any discussion about treatment allocation with patients and clinical observers. Treatment assignment was not revealed until all included subjects had completed 12 months of follow-up. In addition, patients were not unblinded to their treatment assignment if a post treatment intervention was administered.

Outcome measures

The first co-primary endpoint was the efficacy of intradiscal injection of allogeneic BM-MSCs in reducing chronic LBP using the Visual Analogue Scale (VAS) and functional status assessed by the Oswestry Disability Index (ODI)[27] 12 months after treatment, defining strict responders in case of improvement of VAS for pain of at least 20% and 20 mm between baseline and month 12, or improvement of ODI of 20% between baseline and month 12 as shown by the analysis of Ostelo and De Vet.[28] They introduced the concept of a minimally clinically important changes for LBP and suggested that for chronic LBP, a 20 mm change in VAS is a reasonable threshold for significant improvement. This value is based on various studies correlating changes in VAS with global perceived effect scales, establishing that a 20 mm change is both statically and clinically significant.[28]

The secondary co-primary endpoint was the structural efficacy assessed by the disc fluid content measured by quantitative T2 MRI between baseline and month 12. Water content of the discs, determined from T2-weighted sagittal images, was measured in the affected disc segment and in the contiguous 3 to 5 segments above the affected segment. MRI score determination was performed in 5 regions of interest (ROIs) for each disc, 2 for the annulus fibrosus and 3 for the nucleus pulposus. Analysis was performed on the treated disc and two healthy discs as controls. Evaluations were performed before treatment, at 12 and 24 months post-treatment, calculating the T2 relaxation time of each ROI and expressed as a percentage of the initial value.

The secondary endpoints included: (1) VAS, ODI and quality of life (SF-36)[29] at 1, 3, 6, 12 and 24 months; (2) minimal clinically important difference (MCID) on VAS (30% improvement),[28] ODI (10 points improvement),[28] and both compared with baseline; (3) the number of sick leave days among patients with active employment at 12 and 24 months; (4) the consumption of medications to relieve pain (type and dose of painkillers); and (5) the immune response associated with allogeneic cell injection (quantification of anti-HLA antibodies) in all patients. Safety endpoints included the number of adverse events (AEs) and percentage of patients experienced AE, serious AE (SAE) and events of interest related to the procedure such as infection, bleeding, nerve irritation and nerve injury with possible consequences of paresthesia and paralysis.

Assessment of the allogeneic immune response

We evaluated the immunogenicity of the allogeneic BM-MSC treatment by assessing donor specificities of anti-HLA class I and class II antibodies in patients injected with BM-MSCs prior to and 6 months after treatment. DNA was extracted from BM-MSC batches and HLA-A, B, C, DRB1, DRB3/4/5, DQA1, DQB1, DPB1 genotyping was performed using Holotype reagents (Omixon) and the Illumina MiSeq platform. We used the second field resolution level according to the WHO HLA nomenclature (www.HLAnomenclature@hla.alleles.org). At this resolution level, all alleles with the same name code for the same specific HLA molecule. Anti-HLA alloantibodies were then evaluated by single antigen beads using Luminex technology. Briefly, each patient serum was mixed with microbeads coated with a single purified Class l or Class II HLA antigen (Labscreen Single Antigen, One Lambda) and read using a Luminex array analyser (LABScan 200 platform). Reactivity was expressed as raw mean fluorescence intensity (MFI) values and a MFI of 2000 was used as the cut-off for positivity based on historical data and recommendations of Agence de la Biomédecine for organ transplantation to identify the unacceptable donor antigens for a HLA sensitised recipient and to our previous study on BM-MSC-induced alloreactivity.[30]

Sample size calculation

The sample size calculation was based on the findings of the Mesoblast trial.[19] We assumed a clinical responder rate at 12 months of 30% in the control group and 60% in the treatment group. Sample size for the two co-primary endpoints was calculated to obtain a power of 90% leading to a bilateral alpha risk assessment of 5% in balanced groups. At this level, the power of the study was assessed as being in the range 81% to 90%, subject to the co-dependence of the two co-primary endpoints. Taking into account an estimated inclusion failure of 10%, it was necessary to include 56 individuals per group (total 112 subjects).

Statistical analysis

The primary outcome was analysed according to the intention-to-treat principle after a multiple imputation of missing data[31] based on fully conditional specification method. Thirty datasets were imputed corresponding to as many imputations as the percentage of patients with at least one missing data among the variables involved in the multiple imputation (sociodemographic and medical history, current painkillers, pain, disability and quality of life at each visit, randomisation arm). Univariate logistic models were performed to compared primary outcome between groups on each imputed database and summarised using Rubin's rule to obtain the OR, CI and p value of the effect of the intervention on the clinical co-primary outcome.[32]

As we had too many missing data on the anatomical co-primary endpoint, we only performed a descriptive analysis. Sensitivity analysis of the primary outcome and all secondary analyses were performed on the full analysis set, that is, without imputation of missing data, with censoring of data in patients with major protocol deviation, and with analysis in the administration arm.

To analyse the evolution of pain, disability and quality of life throughout the study, we used linear mixed models with random intercept, including discrete time, group and interaction time*group as fixed effects. We computed the adjusted mean differences of scales between each time and baseline, and the p values of these differences were corrected using the false discovery rate algorithm. The same strategy was used with logistic mixed models and adjusted proportion differences for the evolution of the rate of patients achieving the MCID. We used the SAS software V.9.04 (SAS Institute) and R software V.4.3.1.

RESULTS

Demographic and clinical characteristics

An outline of the study design together with the number of participants involved at each timepoint is shown (figure 1). In total, 114 of the 152 screened patients were enrolled between April 2018 and April 2021, and were randomised with 58 patients in the allogeneic BM-MSC group and 56 patients in the sham placebo group. All patients were included in the intention-to-treat analysis and two were excluded in the full analysis set. One patient was excluded because they withdrew consent before injection, and the other because they were unblinded before the end of study. In each group, two patients received the treatment of the other group. We decided to analyse these patients based on the actual treatment they received.

Baseline characteristics of the 114 patients were similar between both groups and are shown in detail in table 1: patients were predominantly male (65%), with a mean age of 40.9 years (± 8.89), mainly currently employed (>90%), had a sick leave due to IDD in less than 25% of cases, had mean pain intensity on VAS of 59.2 (± 16.75) mm and had mean ODI score of 29.9 (± 12.9) on a 0–100% scale.

Primary outcome

At 12 months after the intervention, the percentage of responders was 74% of patients in the experimental group vs 68.8% in the placebo group (table 2). The odds of being a responder for patients in the allogeneic BM-MSC group is 1.23 times higher than for patients in the placebo group (0.32–2.88, p=0.64). At month 12, MRI data were available for 55 patients (30 in the treatment group and 25 in the placebo group). The change in disc fluid content suggestive of disc regeneration between baseline and month 12 was an average of 41.7% in the placebo group vs 37.9% in the treatment group (data not significant, table 3).

Secondary outcomes

For pain assessment using VAS, we observed an improvement in all time points in both groups (table 2). There was no statistically significant beneficial effect of allogeneic BM-MSC on LBP intensity (VAS) at the different secondary time points (1, 3, 6, 12 and 24 months) in the full analysis

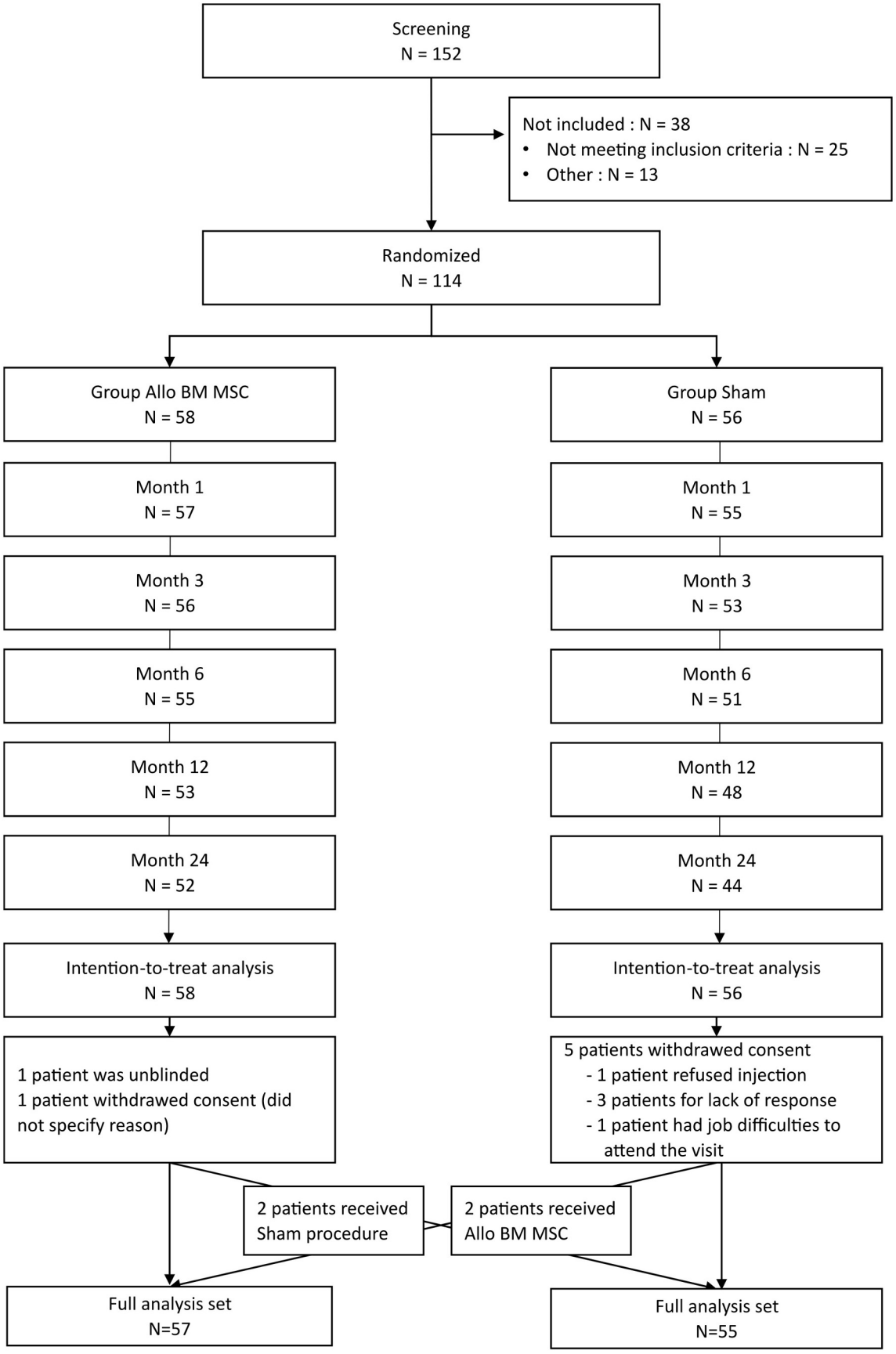

Figure 1 Flow chart of the RESPINE study. BM-MSC, bone marrow mesenchymal stromal cell.

Table 1 Baseline characteristics of patients with chronic LBP associated with IDD

Characteristics	Allogeneic BM-MSC group (N=58)	Sham control group (N=56)	Difference (95% CI)
Mean age (SD), years	42.9 (± 8.8)	38.7 (± 8.6)	4.22 (1.00; 7.43)*
Female, n/N (%)	21/58 (36.2)	18/56 (32.1)	4.06 (–13.33; 21.46)
Active smokers, n/N (%)	15/52 (26.8)	14/50 (25.9)	0.86 (–15.61; 17.33)
Median body mass index (IQR), kg/m²	24.5 (22.9; 26.9)	24.3 (22.6; 27.3)	0.46 (–0.79; 1.75)
Educational level, n/N (%)			
Primary school (at least 5 years of education)	8/56 (14.3)	4/54 (7.4)	6.88 (–4.65; 18.40)
Secondary school (at least 9 years of education)	18/56 (32.1)	18/54 (33.3)	–1.19 (–18.73; 16.35)
College (at least 12 years of education)	11/56 (19.6)	10/54 (18.5)	1.12 (–13.56; 15.81)
License (at least 15 years of education)	10/56 (17.9)	15/54 (27.8)	–9.92 (–25.52; 5.68)
Master (at least 17 years of education)	9/56 (16.07)	6/54 (11.1)	4.96 (–7.80; 17.72)
Doctor (at least 20 years of education)	0/56 (0.0)	1/54 (1.8)	–1.85 (–5.45; 1.74)
Employment status, n/N (%)			
Full-time or part-time employment	54/58 (93.1)	50/55 (90.9)	2.19 (–7.82; 12.21)
Unemployed	2/58 (3.4)	5/55 (9.1)	–5.64 (–14.57; 3.29)
Retired	2/58 (3.4)	0/55 (0.0)	3.45 (–1.25; 8.14)
Sick leave for IDD, n/N (%)	8/33 (24.2)	4/34 (11.8)	12.48 (–5.72; 30.67)
Mean LBP pain intensity on VAS (range, 0–100)	59.4 (± 16.1)	59.1 (± 17.6)	0.33 (–5.92; 6.57)
Median Schober test score (IQR), cm	4.3 (2.5; 5.0)	4.0 (2.5; 5.0)	0.00 (–1.00; 1.00)
Median finger-to-floor test score, (IQR), cm	15.0 (5.0; 25.0)	15.0 (5.0; 25.0)	0.00 (–5.00; 5.00)
Current therapy at baseline, n/N (%)			
Non-pharmacological treatment	9/58 (15.5)	6/56 (10.7)	
Analgesics (all grade) or NSAIDs	24/58 (41.4)	18/56 (32.1)	9.24 (–8.38; 26.85)
NSAIDS or grade1 analgesics	20/58 (34.5)	15/56 (26.8)	7.70 (–9.16; 24.55)
Grade2 analgesics	17/58 (29.3)	11/56 (19.6)	9.67 (–6.00; 25.34)
Mean ODI score (SD) (range 0–100%)	28.9 (± 12.8)	30.9 (± 13.0)	–1.98 (–6.77; 2.81)
Mean ODI score (SD) (range 0–50)	14.5 (± 6.4)	15.4 (± 6.5)	–0.99 (–3.39; 1.41)
ODI subscores, n/N (%)			
No disability (0–4)	2/58 (3.4)	2/56 (3.6)	–0.06 (–6.88; 6.75)
Mild disability (5–14)	28/58 (48.3)	23/56 (41.1)	8.05 (–10.24; 26.34)
Moderate disability (15–24)	23/58 (39.6)	25/56 (44.6)	–4.29 (–22.51; 13.92)
Severe disability (25–24)	4/58 (6.9)	6/56 (10.7)	–3.70 (–14.17; 6.77)
Completely disabled (35–50)	0/58 (0.0)	0/56 (0.0)	NA
Median SF-36 score (SD) (range, 0–100)			
Physical component	37.2 (32.2; 42.0)	36.1 (29.5; 40.0)	–1.30 (–4.07; 1.57)
Mental component	38.2 (33.9; 47.7)	39.5 (30.8; 51.8)	–0.62 (–4.63; 3.93)
Modified Pfirmann degenerative scale, (%)			
Grade IV	10/27 (37.0)	8/27 (29.6)	7.41 (–17.66; 32.48)
Grade V	16/27 (59.3)	1/27 (59.3)	0.00 (–26.21; 26.21)
Grade VI	1/27 (3.7)	3/27 (11.1)	–7.41 (–21.24; 6.42)
Treated vertebral level, (%)			
L3-L4	10.7	3.7	7.01 (–6.48; 20.50)
L4-L5	25.0	29.6	–4.63 (–28.16; 18.91)
L5-S1	64.3	66.7	–2.38 (–27.50; 22.74)

Values are n (%) or mean±SD or median (Q1; Q3).

*Difference statistically significant.
.BM-MSC, bone marrow mesenchymal stromal cells; IDD, intervertebral disc disease; LBP, low back pain; NSAIDs, non-steroidal anti-inflammatory drugs; ODI, Oswestry Disability Index; SF-36, Short Form 36 health survey; VAS, Visual Analogue Scale.

set. At 12 months, the adjusted mean difference in pain VAS was −10.5 (±4.7) mm between the allogeneic BM-MSC group and the placebo group (p=0.15). All the secondary outcomes (ODI, SF-36) showed no significant differences between groups (figure 2, table 2).

The proportion of patients reaching the MCID in VAS pain score (30% improvement) between baseline and 1 3 6 12 and 24 months were slightly elevated in the BM-MSC group but not statistically significant. The same result was seen in the proportion of patients reaching the MCID in ODI score (10 point improvement; table 2). The number of patients on sick leave was similar between baseline, 12 and 24 months (eight patients in the BM-MSC group and four patients in the placebo group). No difference in medication intake, either painkillers or NSAIDs was observed between the two arms throughout the study. Regarding the allogeneic immune response, we found 5 out of 50 patients who developed de novo donor specific antibodies (see in online supplemental tables 6–7). As shown in online supplemental figure 3 and 4, MRI follow-up of the treated disc at 12 months did not find any differences with disc fluid-content and modified Pfirrmann staging between the

Table 2 Evolution of pain, disability and quality of life throughout the study, comparatively to baseline in the full analysis set

Variable	Allogeneic BM-MSC	Sham	Adjusted mean or proportion difference±SD	Corrected P value
Primary outcome				
M1 vs baseline (N=109)	30 (54.55)	21 (38.89)	0.26 (±0.16)	0.46
M3 vs baseline (N=106)	35 (63.64)	32 (62.75)	0.04 (±0.14)	0.77
M6 vs baseline (N=104)	38 (70.37)	32 (64.00)	0.10 (±0.12)	0.77
M12 vs baseline (N=98)	37 (74.00)	33 (68.75)	0.05 (±0.10)	0.77
M24 vs baseline (N=94)	38 (76.00)	33 (75.00)	0.06 (±0.09)	0.77
Secondary outcomes				
Pain VAS at month 1 (N=110)	49.24 (±24.33)	49.80 (±22.65)	−0.55 (±4.49)	0.99
Pain VAS at month 3 (N=106)	45.33 (±25.98)	47.29 (±23.55)	−1.81 (±4.55)	0.99
Pain VAS at month 6 (N=104)	39.72 (±25.87)	41.98 (±24.29)	−2.91 (±4.58)	0.99
Pain VAS at month 12 (N=98)	33.68 (±27.20)	43.06 (±25.12)	−10.55 (±4.68)	0.15
Pain VAS at month 24 (N=94)	31.96 (±25.02)	34.41 (±23.67)	−4.65 (±4.75)	0.99
ODI score at month 1 (N=109)	25.08 (±16.67)	27.81 (±14.95)	−2.24 (±2.88)	0.52
ODI score at month 3 (N=107)	21.45 (±16.07)	23.92 (±15.68)	−2.81 (±2.89)	0.50
ODI score at month 6 (N=105)	18.70 (±13.42)	22.59 (±15.56)	−3.67 (±2.90)	0.42
ODI score at month 12 (N=98)	16.76 (±14.50)	21.08 (±15.63)	−4.39 (±2.95)	0.41
ODI score at month 24 (N=94)	16.23 (±16.07)	19.41 (±15.43)	−4.46 (±2.98)	0.41
MCS (SF-36) at month 1 (N=109)	42.41 (±10.38)	41.45 (±10.92)	1.16 (±2.18)	0.89
MCS (SF-36) at month 3 (N=106)	45.26 (±10.57)	42.15 (±11.05)	3.44 (±2.20)	0.72
MCS (SF-36) at month 6 (N=102)	44.77 (±10.49)	42.72 (±10.58)	2.31 (±2.22)	0.75
MCS (SF-36) at month 12 (N=97)	44.97 (±11.47)	42.67 (±13.04)	2.00 (±2.25)	0.75
MCS (SF-36) at month 24 (N=94)	43.68 (±13.34)	44.06 (±12.22)	−0.67 (±2.27)	0.92
PCS (SF-36) at month 1 (N=109)	38.08 (±7.96)	37.09 (±8.34)	0.75 (±1.69)	0.66
PCS (SF-36) at month 3 (N=106)	40.31 (±8.59)	38.59 (±8.09)	1.52 (±1.70)	0.66
PCS (SF-36) at month 6 (N=102)	41.59 (±9.45)	40.69 (±9.49)	1.05 (±1.72)	0.66
PCS (SF-36) at month 12 (N=97)	43.37 (±10.31)	40.21 (±9.41)	3.27 (±1.74)	0.37
PCS (SF-36) at month 24 (N=94)	42.89 (±9.26)	41.61 (±10.02)	1.82 (±1.75)	0.66
30% Pain VAS improvement, M1 vs baseline (N=110)	20 (36.36)	16 (29.09)	0.09 (±0.11)	0.54
30% Pain VAS improvement, M3 vs baseline (N=106)	21 (38.18)	21 (41.18)	−0.05 (±0.14)	0.71
30% Pain VAS improvement, M6 vs baseline (N=104)	30 (55.56)	22 (44.00)	0.18 (±0.15)	0.35
30% Pain VAS improvement, M12 vs baseline (N=98)	30 (60.00)	18 (37.50)	0.34 (±0.14)	0.08
30% Pain VAS improvement, M24 vs baseline (N=94)	33 (66.00)	26 (59.09)	0.17 (± 0.14	0.35
10-point improvement of ODI, M1 vs baseline (N=109)	13 (23.64)	10 (18.52)	0.05 (±0.07)	0.51
10-point improvement of ODI, M3 vs baseline (N=107)	23 (41.82)	18 (34.62)	0.12 (±0.14)	0.51
10-point improvement of ODI, M6 vs baseline (N=105)	28 (51.85)	22 (43.14)	0.13 (±0.16)	0.51
10-point improvement of ODI, M12 vs baseline (N=98)	30 (60.00)	21 (43.75)	0.26 (±0.15)	0.48
10-point improvement of ODI, M24 vs baseline (N=94)	29 (58.00)	24 (54.55)	0.11 (±0.16)	0.51
30% VAS improvement and 10 points of ODI, M1 vs baseline (N=109)	12 (21.82)	8 (14.81)	0.06 (±0.06)	0.41
30% VAS improvement and 10 points of ODI, M3 vs baseline (N=107)	16 (29.09)	13 (25.00)	0.05 (±0.09)	0.60
30% VAS improvement and 10 points of ODI, M6 vs baseline (N=105)	22 (40.74)	15 (29.41)	0.15 (±0.13)	0.39
30% VAS improvement and 10 points of ODI, M12 vs baseline (N=98)	23 (46.00)	14 (29.17)	0.25 (±0.14)	0.33
30% VAS improvement and 10 points of ODI, M24 vs baseline (N=94)	26 (52.00)	19 (43.18)	0.22 (±0.16)	0.39

Values are n(%) or mean±SD. Adjusted mean (or proportion) differences and their SD are computed in linear (or logistic) mixed models with random intercept, including discrete time, group and interaction time*group as fixed effects. P values are corrected using the false discovery rate algorithm, separately for each outcome.
BM-MSC, bone marrow mesenchymal stromal cell; MCS, Mental Summary Score (SF-36); ODI, Oswestry Disability Index; PCS, Physical Summary Score (SF-36); VAS, Visual Analogue Scale.

2 arms (table 3, online supplemental table 8). In contrast, we observed after 2 years an increase in the water content signal in the BM-MSC group compared with placebo (115% vs 93.2% of initial value, non-significant).

Safety assessment

The treatment groups did not show significant differences in terms of AEs and SAEs. Throughout the study, a total of 488 AEs occurring in 84 patients were reported (272 in the allogeneic BM-MSC group; 216 AEs in the placebo group). The median number of total AE was similar in each group. Causality was assessed as being due to study medication in 20 AEs (17 patients) in the BM-MSC group and 24 AEs (9 patients) in the placebo group. We did not observed AEs such as lumbar surgery, IVD calcification or infectious spondylodiscitis.

A total of 18 SAEs were reported up to 24 months (10 for 7 patients in the BM-MSC group and 8 for 7 patients in the placebo group) with no significant difference between the groups. No SAEs led to discontinuation, and four were considered to be related to the study agent or injection procedure: three patients in the cell-treated group and two in the placebo group experienced serious but transient LBP worsening. The safety profile is summarised in tables 4 and 5.

Table 3 MRI analysis of disc fluid content, in % of baseline disc fluid content and modified Pfirrmann degenerative scale between 12/24 months and baseline

	Evolution of disc-fluid content	Allogeneic BM-MSC	Sham	P value
M12 vs baseline (N=53*)	Mean (±SD)	−5.15 (±20.22)	−1.16 (±18.57)	0.77
	Disc regeneration (evolution>0%)	11 (37.93)	10 (41.67)	
	No evolution (evolution=0%)	1 (3.45)	2 (8.33)	
	Disc degeneration (evolution<0%)	17 (58.62)	12 (50.00)	
M24 vs baseline (N=20)	Mean (±SD)	4.58 (±18.14)	−1.44 (±25.35)	0.55
	Disc regeneration (evolution>0%)	8 (61.54)	3 (42.86)	
	No evolution (evolution=0%)	0 (0.00)	0 (0.00)	
	Disc degeneration (evolution<0%)	5 (38.46)	4 (57.14)	
Changes in modified Pfirmann score between M12 and baseline (N=53*), n/N (%)				0.94
	Improvement	9/29 (31.1)	8/24 (33.4)	
	No change	15/29 (51.7)	11/24 (45.8)	
	Progression	5/29 (17.2)	5/24 (20.8)	

*Two patients were excluded from the analysis because their consent had been withdrawn at 12 months. Values are n (%) or mean±SD.
BM-MSC, bone marrow mesenchymal stromal cell.

DISCUSSION

BM-MSC represents a promising opportunity for the biological treatment of IDD, but only high-quality randomised controlled trials, comparing it to standard care, can determine whether it is a truly effective alternative to spine fusion or disc replacement. The RESPINE trial is one of a few studies investigating the efficacy of allogeneic BM-MSC in the treatment of IDD. The methodology used in the RESPINE double-blind trial was robust. Subjects, radiographic reviewers and rheumatologists assessing the clinical response were blinded to the treatment assignment, thus limiting the source of bias. Only the radiologists in charge of the disc injection were not blinded. We report the first double-blind controlled trial comparing injection of allogeneic BM-MSC to placebo in 114 patients affected by chronic LBP due to single-level IDD. The clinical results demonstrated a progressive improvement of functional and pain indices by 70% within 6 months and by 74–76% at months 12 and 24. The probability of being a responder for patients in the BM-MSC group was higher than for patients in the sham group, although not significant. The MSC-treated group had greater proportions of subjects at most thresholds, but particularly 60% of patients in the BM-MSC-treated arm achieved the pain MCID compared with the control group at month 12. Despite the robust trial design and the favourable premise of MSC therapy, the primary endpoint of significant improvement compared with placebo was not achieved. This outcome necessitates a critical examination of the trial context within the broader landscape of IDD treatments and the implications of our findings. While our study did not conclusively demonstrate the efficacy of allogeneic BM-MSC for IDD treatment, it nonetheless contributes

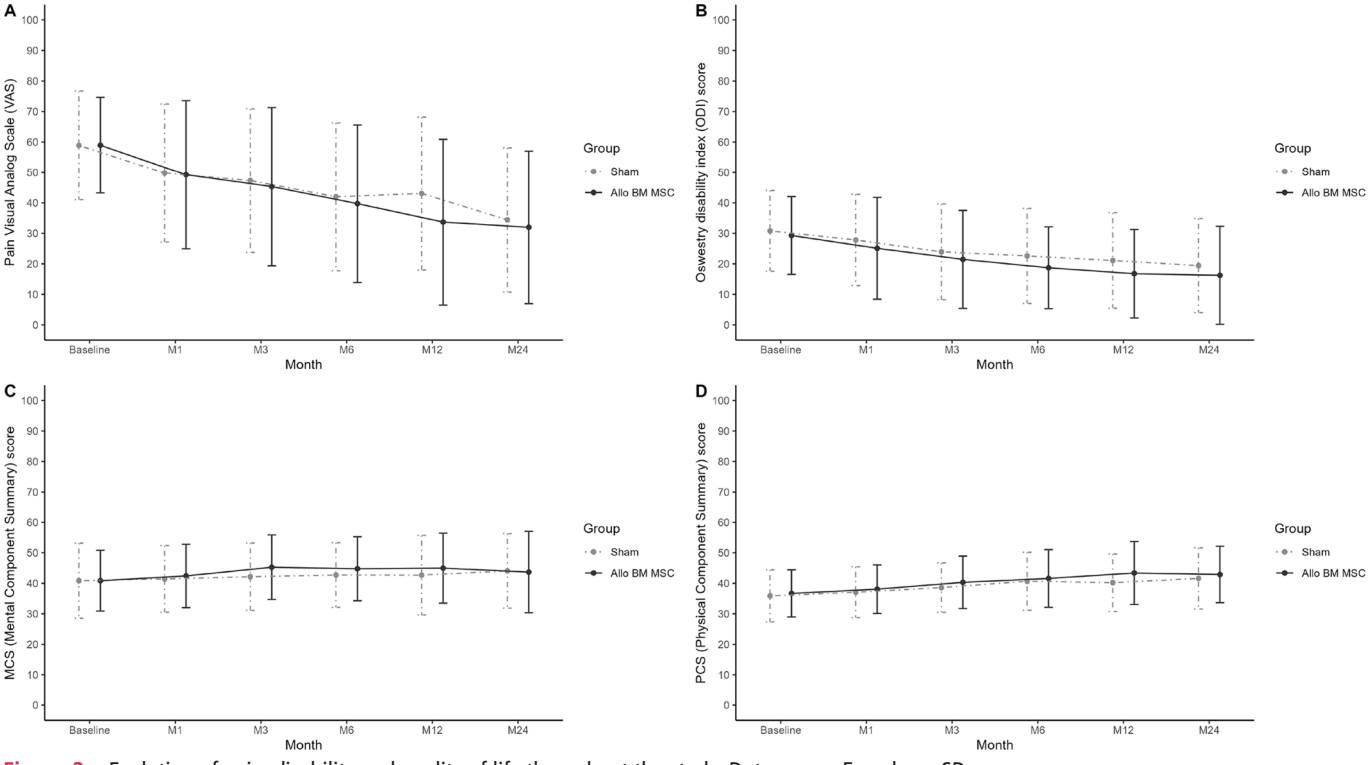

Figure 2 Evolution of pain, disability and quality of life throughout the study. Dots: mean. Error bars: SD.

Table 4 Safety profile during 24-month follow-up

Variables	Allogeneic BM-MSC group (N=58)	Sham control group (N=56)
Time of occurrence after treatment, n/N (%)		
Between screening and baseline	9	10
Before 1 month	49	48
1–3 months	28	29
3–6 months	44	33
6–12 months	53	39
12–24 months	74	40
Type of serious adverse events, n/N (%)		
Hospitalisations for usual care of chronic LBP	0	0
Hospitalisations for events unrelated to chronic LBP	3	5
Events related to chronic LBP without hospitalisation	0	0
Events unrelated to chronic LBP without hospitalisation	0	4
Deaths	0	0
Undefined	5	1

BM-MSC, bone marrow mesenchymal stromal cell; LBP, low back pain.

valuable insights into the complexities of MSC therapy in a challenging clinical context. It is also possible that other cell types, for example nucleus pulposus cells (NPCs) or cell-derived products such as extracellular vesicles (EVs) may provide a more effective outcome. Indeed, Han *et al* demonstrated superiority of NPC over MSC in a rat IDD model.[33] Ambrosio *et al* also demonstrated that NPC-derived EVs were superior to MSC-derived EVs in preserving disc height and preventing degenerative changes in a rat IDD model.[34] These observations point to the criticality of cell type in eliciting a regenerative response in IDD, as discussed by Williams *et al*.[35] However, although rodent studies provide useful information about promising therapeutic strategies, the selection of the optimal cell type can only be determined by patient trials of sufficient scale and robust design. The societal impact of chronic LBP is significant, with incapacity, loss of working days and high expenditure for healthcare. The need for innovative treatments is therefore urgent.

Table 5 Serious adverse events observed during the 24-month follow-up

SAE categories	Allogeneic BM-MSC group (N=8)	Sham control group (N=10)
Musculoskeletal disorders		
Exacerbation of LBP	4	2
Fibromyalgia		1
Hip osteoarthritis	1	
Cervical surgery		1
Fracture		2
Nervous system disorders		
Vagus syndrome		1
Infections		
COVID-19	1	
Oncologic disorders		
Brest cancer	1	
Psychiatric disorders		
Depression		1
Obstetrical disorders		
Pregnancy		1
Caesarean delivery		1
Uterus fibroma surgery	1	

N is the number of serious adverse events. One patient in the allogeneic BM-MSC group and three patients in the sham control group had two serious adverse events.
BM-MSC, bone marrow mesenchymal stromal cell; LBP, low back pain; SAE, serious adverse event.

Our results align with previous clinical studies of intradiscal injection of MSCs for IDD.[17 18 22 36] Orozco *et al* reported that 10 patients suffering from chronic IDD who were injected intradiscally with autologous BM-MSCs exhibited rapid and progressive improvement of functional indexes that approached 65% to 78% by 1 year.[17] Noriega *et al* reported long-term assessments of allogenic MSC injection in single level IDD in 23 subjects.[18 22] In their study, improvements in pain and the ODI persisted 3.5 years later. A large prospective, single-blind, controlled clinical study with allogeneic adult Stro1/3+ mesenchymal precursor cells (MPCs) combined with hyaluronic acid enrolled 100 patients with cLBP caused by moderate single level IDD (modified Pfirrmann score 3–6). Patients were randomised to receive direct intradiscal injections of saline, hyaluronic acid, or two doses of MPCs in a hyaluronic acid carrier, of 6 million or 18 million.[19] Results at month 12 showed that surgical interventions, revealing failure of the treatment, were reduced in the cell-treated groups. In these groups, 62% of the patients achieved a 50% reduction in pain while the control groups achieved only 35%. Functional assessment through the ODI score revealed a greater percentage of patients with at least a 30% reduction in the cell-treated groups (62%) compared with controls (41%). Despite appropriate methodology, the study failed to achieve the primary endpoint. In addition, a recent meta-analysis underlines that MSC-therapy may be effective in relieving pain and improving ODI score significantly in patients with lumbar discogenic pain. They raised that MSC therapy may also be associated with a lower risk of adverse events and reoperation rates.[36]

We observed an increase in the proportion of subjects achieving the MCID composite endpoints for the cell-treated groups compared with the sham at month 12 but did not reach statistical significance, related to the high level of placebo effect. Indeed, the placebo effect has been very strong in studies of other fields where cell therapies were used.[37] The substantial placebo effect observed in our study aligns with existing literature showing strong placebo responses in trials involving pain and mobility assessments. Such effects could overshadow modest but clinically meaningful benefits of new treatments. This phenomenon is particularly notable in IDD, where psychological factors significantly influence pain perception and treatment responsiveness.[38] Future trials should consider methodologies that might better discriminate between placebo effects and the therapeutic action of the treatment, such as more refined patient selection or enhanced blinding and placebo control mechanisms.

Concerning imaging data, lumbar MRI T2 relaxation measurements demonstrated an improvement in the water content of the disc at month 24 but not at month 12, suggesting an increase in proteoglycan and structural improvement in the long term. This is in line with improvements of cartilage signal observed after MSC injection in the knee joint.[39] The failure to meet the primary endpoint brings into question the potency of MSC therapies. While MSC therapies have shown potential in preclinical studies, translating these effects into clinical benefits has proven challenging. This discrepancy could be due to variations in the pathophysiology of IDD among patients, which were not fully accounted for in our trial's design. Future studies might explore

a stratified approach, targeting patient subgroups more likely to respond based on specific biological markers or disease phenotypes. For example, targeting patients with active discopathy (Modic 1 lesions) with low-grade local and systemic inflammation might be more relevant as it is likely to activate BM-MSCs.

Comparatively, our findings contrast with some smaller-scale studies or those using autologous MSCs, which have reported more favourable outcomes. A systematic evidence-based analysis found that cell therapy provided an average reduction of 3.2 points on the pain scale and 27.0 points on the ODI at 1-year follow-up, with a generally good safety profile.[40] Our study achieved a smaller improvement with a reduction in ODI score of 16.8 points at 12 months. This divergence could stem from inherent differences between autologous and allogeneic MSC therapies, including immunogenicity and cell potency issues, which warrant further investigation. In addition, we did not find any differences in clinical results depending on the type of donor. However, it has been established that MSCs are highly heterogeneous between donors, with the consequences of affecting the main functions of MSCs as well as their secretome.[41] The development of cell therapy requires standardisation of procedures to obtain robust clinical results.

The findings reported in this study suggest that there are no apparent safety concerns associated with a single intradiscal injection of MSCs after 24 months of follow-up. Both the procedure and the treatment were well tolerated, with no discitis reported in a total of 58 intradiscal injections. Moreover, there were no clinical symptoms of immune reactions to allogeneic MSCs. There was a low rate of treatment-associated SAEs overall, and the rates of these events in the MSC group were not significantly different from the sham group. The use of allogeneic cells was preferred, as this strategy simplified the overall procedure, improving the yields and decreasing costs.[42] One major risk could be considered the potential immune rejection. However, it has been shown repeatedly that MSCs inhibit immune responses, inducing immunologic tolerance.[43] Allogeneic MSCs have been repeatedly proven in animals over the years without any indication of rejection or delayed immune reactions. In the Poseidon trial, a randomised dose-finding comparison study of allogeneic versus autologous MSCs delivered by transendocardial injection of allogeneic or autologous MSCs, the injection of allogeneic MSCs did not stimulate significant donor-specific alloimmune reactions.[44] In our study, only five patients in the allogeneic group showed sensitisation at the 6-month time point. Our results are in line with the majority of recent clinical trials dealing with allogeneic-MSC showing about 10% of patients with DSA positivity.[30 45]

However, our study had some limitations. We collected only MRI results from 55 subjects across 2 study arms. This resulted in a relatively small number of subjects in each arm, which limited statistical power. The duration of follow-up in our study was another point of concern. While we monitored patients up to 24 months post-treatment, IDD is a progressively degenerative condition, and longer observation periods may be necessary to fully capture the long-term efficacy and safety of MSC therapies. Moreover, a bias in selection of the patients cannot be excluded. Indeed, selection of the patients in the context of cLBP due to single level IDD is very challenging. Several anatomopathological features are recognised as causes of cLBP, some even extrinsic to the spine.[46] For safety reasons, we did not perform discography in this study[47] and therefore we cannot discount the possibility misdiagnosis of patients that received the BM-MSC injection. Therefore, single level IDD may not be the sole cause of LBP in our cohort of patients.

CONCLUSION

In conclusion, while our study did not conclusively demonstrate the efficacy of allogeneic BM-MSCs for IDD treatment, it contributes valuable insights into the complexities of MSC therapy in a challenging clinical context. Our study highlights the overall safety and potential of allogeneic BM-MSC intradiscal transplantation to alleviate LBP. Further research should aim not only to refine MSC therapies but also to explore combinatory approaches that address the multifactorial nature of disc degeneration and chronic pain.

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