Biologic Treatments for Spinal Disc Regeneration

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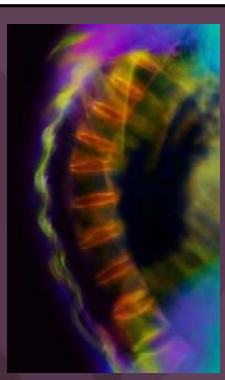

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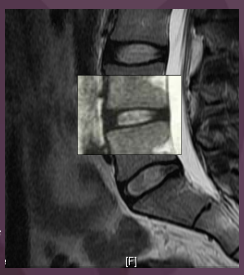
Chronic Axial Lumbar Back Pain
Patient profile

- 12.5M Patients annually present with chronic (>6 months), low back pain in the United States
- Only 20% present with evidence of an easily imaged pathology or anatomic source of pain

- 10M U.S. patients annually present with symptoms of discogenic pain:
  - *Chronic axial low back pain (> 6 months)*
  - *Referred leg pain that is less than back pain*
  - *Mild to moderate disc generation at 1 or more adjacent levels*
  - *No significant instability or disc height loss*
  - *Minimal central canal or foraminal stenosis*



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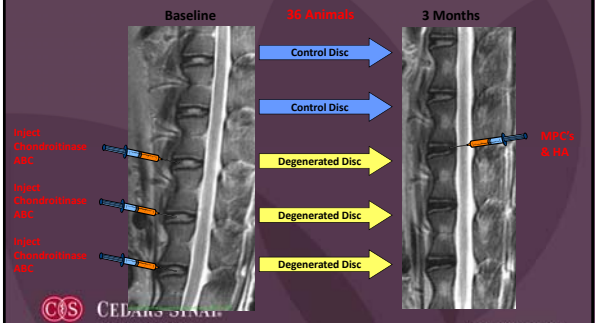
Intervertebral Disc Repair – Preclinical Study



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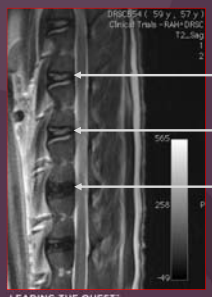
Intervertebral Disc Repair – Preclinical Study

MRI 6 months after injecting 0.5 million MPC showing similar H_2O signal (white) to normal control ovine disc



Non-Degenerated Control Disc

MPC+HA Treated Disc

Degenerated Disc (No Treatment)

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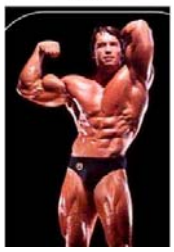
Human Spinal Disease

THEN



I'll Be BACK

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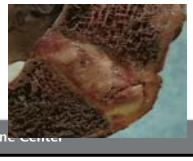
Human Spinal Disease

NOW

Oh My BACK



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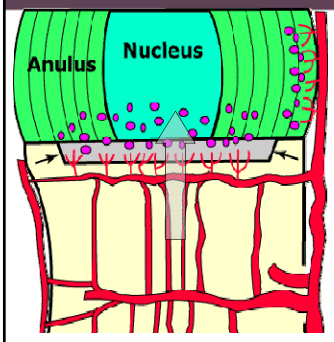
Structure and Vascularity of the Disc

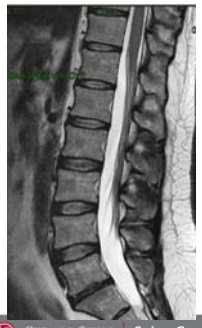


Nucleus pulposus poorly vascularized

- No blood vessels penetrate the inner annulus
- Pressure on the nucleus is 5-15 times greater than blood pressure.
- It is hypothesized that the tissue is hypoxic.

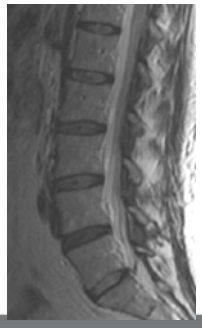
OP-1 BMPS rhGDF-5

Pre-Op MRI



CAL 03-019

Pre-Op MRI



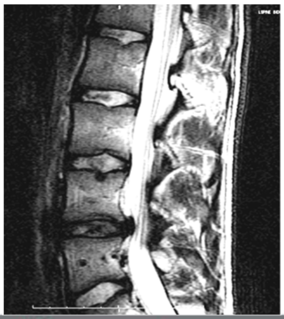
BSF 03-020

Fibrin Glue Study

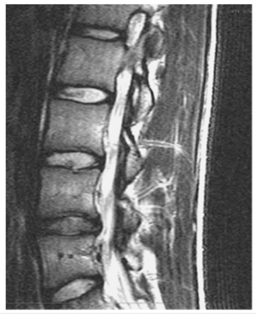
- Clinical Study
  - Biostat System
    - Phase III
    - Internal disc disruptions (IDD) of lumbar intervertebral discs
    - 15 sites, N=260
    - One or two level, randomized, blinded
    - First patient in February 2010

MRI L4-5 Disc Degeneration,
Example pt treated with Fibrin Sealant

pre injection



post injection follow-up



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11-003 wdo Fibrin Sealant

VAS Low Back Pain

26 Weeks

Biostat	***26% improvement***
Saline	***88% improvement***

Marginal

p = 0.056

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Is there Clinical Improvement Associated with Saline Injection for Discogenic Low Back Pain: Comparison of RCT Outcomes

Hyun W. Bae, MD[1,2], Linda E.A. Kanim, MA[1,2], Samantha R. Thordarson,[1] Noelle Provenzano,[1] Janice Kim, BA[1,2], Evish Kamrava, MD[1,2], Timothy Davis, MD[1,2], Rick Delamarter, MD[1,2]
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INTRODUCTION

Recently, several multicenter clinical trials studying the effect of biologic substances or cell-based injections on lumbar intervertebral disc repair were completed. These studies all included a placebo injection with saline as a control. These studies were randomized, double blinded, and prospective. Their intent was to investigate novel treatment options for intervertebral disc repair. The findings of these studies highlight a possible reduction in pain and disability related to the saline injection.

The purpose of this analysis was to evaluate saline injection related patient reported outcomes from multiple intervertebral disc injection studies. All patients were seen at same institution.

METHODS

A post hoc comparison was performed using data derived from four similar studies conducted at a single site that were prospective, randomized controlled, and double-blinded. Standard across the studies (A, B, C, D), patients were only included if they had symptomatic disc disease at lumbar levels of L1 to L5/S1, had a positive provocative discography, and failed at least 3 months of nonoperative treatment. Patients (males & females) ranged from 18 to 65 years of age, and were randomized into placebo (saline) or treatment (investigational substance) intervertebral disc injection groups.

Visual Analog Scale for back/buttock pain (VAS, 100-mm line, with 'No Pain' indicated at the left of the horizontal scale and 'Most Severe Pain' at the right end of the scale) and the Oswestry Disability Index (ODI, a Likert type scale calculating functional disability) for low back pain, along with surgeon administered physical exam were completed at pre-treatment visit (pretx), and at least at 3, 6, 12 months post injection (follow-up, 12mo). Only study B utilized the Roland-Morris Disability (24 items checklist) Questionnaire instead of the Oswestry Questionnaire.
Disability percentage scores were calculated:
Oswestry Disability, the sum of the section scores divided by the total possible score (50 if all sections are completed), and the resulting total was multiplied by 100. Roland Morris Disability, the sum of the checked items divided by 24 multiplied by 100 to yield a percentage score. Mixed model ANOVA was used with factors of visit-time (repeated) and treatment (grouping).

For all studies, side effects and adverse events were systematically

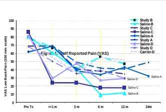

Figure 2. Disability

RESULTS

Control Variables: Gender and age were controlled in the overall analysis. There was a higher percentage of males enrolled across the four studies (61.5% A, 61.5% B, 60% C, 94% D) with 74% males (37/50) in the combined analysis.

Males reported slightly less VAS improvement as well as less VAS pain than females preoperatively; This difference was not significant. (Males: 66.8 mm VAS pain at pretx, 39.6 mm VAS pain at 12 months post treatment, with a 41.5% difference.

Females: 81.3 mm VAS pain at pretx, 32.4 mm VAS pain with a 40.6% average difference at 12 months post treatment). Age was only related to VAS at 12 months ($p < 0.04$, $r=0.31$, 9.6% of common variability).

Across the studies, by 12 months, there was average 58.5% less VAS pain for saline injected patients compared to 36.6% less pain for investigational treatment injected patients (S: 20.4 mm vs. I:37.7mm $p<0.01$, ANOVA controlling for age, gender, study).

Additionally, across the studies there was a statistically significant main effect of decrease in VAS pain for both the investigational treatment or saline injected patients ($p<0.004$ at 3 months; $p<0.007$ at 6 months; $p<0.0001$, 12 months compared to pre-treatment).

For Disability, saline injected patients reported significantly less Disability than investigational treatment only in Study B (6 mo, $p<0.04$; 12 mo $p<0.05$).

DISCUSSION

An intervertebral disc injection regimen of saline may offer patients a chance for some pain resolution, decreased disability, or may merely introduce less substance reaction than to treatment or carriers and injection trauma. Noting the 50% or greater improvement observed for saline injected patients in this study provides a potentially higher threshold and means to define the MCID for injection type intervertebral disc repair treatments. Independent from the underlying reason for the observation herein, future injection studies now have a high baseline improvement threshold. A more thorough understanding of the "Saline Effect" and possible mechanism of action is needed.

Future directions include:

- Testing for "Saline Effect" in an independent sample, with more patients, and a longer follow-up period.
- Differentiate between a placebo effect and a true saline effect using sham procedures* in future clinical injection studies.

Significance:

Although the intent was to investigate novel treatment options for intervertebral disc repair, results from these trials have elucidated a possible saline effect of improvement in self-reported VAS pain.

Saline-associated clinical improvement provides a threshold for novel treatments to improve upon!

Further research is needed to determine a biologic mechanism for the saline-associated improvement.

REFERENCES

1: Mavrogonatou E, Kletsas D. Differential response of nucleus pulposus intervertebral disc cells to high salt, sorbitol, and urea. J Cell Physiol. 2012 Mar;227(3):1179-87.

2: Fukui S, Iwashita N, Nitta K, Tomie H, Nosaka S. The results of percutaneous intradiscal high-pressure injection of saline in patients with extruded lumbar herniated disc: comparison with microendoscopic discectomy. Pain Med. 2012 Jun;13(6):762-8.

* Current Randomized Clinical Trial Designs include a sham treatment group when evaluating treatments for intervertebral disc repair.

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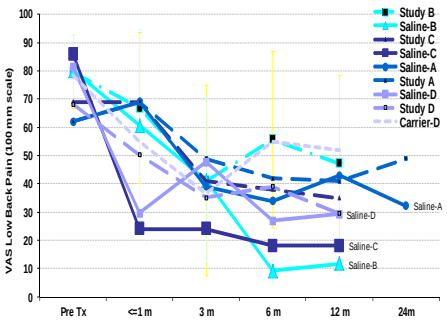
VAS Low Back Pain



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Results

- Four RCT using saline as control
- 58.5% decrease in patients at 12 months treated with saline
- 36.6% decrease in patients at 12 months treated with investigational drug
- $p<0.04$

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Allogeneic Stem Cells– The Future?

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Bioreactor Cell Processing

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Commercial Viability

UBER

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mesoblast — Phase II Results

mesoblast
the adult stem cell company

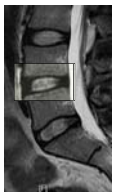
POSITIVE SPINAL DISC REPAIR TRIAL RESULTS USING MESOBLAST ADULT STEM CELLS

Single Injection of Mesenchymal Precursor Cells into Degenerating Intervertebral Discs Reduced Low Back Pain and Improved Function for at Least 12 Months

New York, USA, 29 January and Melbourne, Australia; 30 January 2014: Regenerative medicine company Mesoblast Limited (ASX:MSB; USOTC:MBLTY) today announced positive 12 month outcome results from the 100-patient Phase 2 clinical trial of its proprietary allogeneic, or "off-the-shelf", Mesenchymal Precursor Cells (MPCs) in patients with chronic moderate to severe discogenic low back pain.

The results showed that a single injection of MPCs into degenerating intervertebral discs reduced low back pain and improved function for at least 12 months. When compared with controls, MPC-treated patients used less opioids for pain relief, had greater radiographically-defined disc stability, and underwent less additional surgical and non-surgical treatment interventions. MPC treatments also appeared to be well tolerated during the study.

Mesoblast Chief Executive Silviu Itescu said: "We are very pleased that in a trial primarily designed to assess the safety of Mesoblast's cells for intervertebral disc repair, we have seen strong indications of sustained efficacy across a broad number of clinical and radiographic parameters after a single intra-disc injection. On the basis of these positive results, Mesoblast plans to meet shortly with regulatory authorities in major jurisdictions, including the United States Food and Drug Administration, to discuss product registration trials for the potential treatment of disc degeneration."



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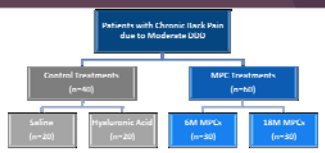
Study Design



- Prospective, multi-center, randomized, double-blind, controlled study
  - Patients and radiographic evaluators blinded to treatment
- Follow-up: 1, 3, 6, 12, 24 & 36 months
- Safety Evaluations
  - Adverse Events
  - Treatment Failure (Surgical & Injection Interventions)
  - Immunological Testing
  - Blood chemistry & inflammatory markers
  - Radiographic
    - Heterotopic ossification
    - Disc degeneration
- Efficacy Evaluations
  - Radiographic Changes
    - MRI
    - X-ray & Stability
  - Lower Back and Leg Pain measured by VAS Score
  - Oswestry Disability Index (ODI)
  - SF-36
  - Work Productivity & Activity Index (WPAI)
  - Medication usage

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Phase 2 Clinical Study Patient Population

A prospective, multicenter, double blinded, controlled clinical study of two doses of immunoselected, culture-expanded, nucleated, allogeneic MPCs when combined with hyaluronic acid in subjects with chronic low back pain (> 6 months) due to moderate DDD at one lumbar level from L1 to S1 and unresponsive to conservative therapy for at least 3 months (including physical therapy) and evalauted at 1, 3, 6, 12, 24 & 36 months.

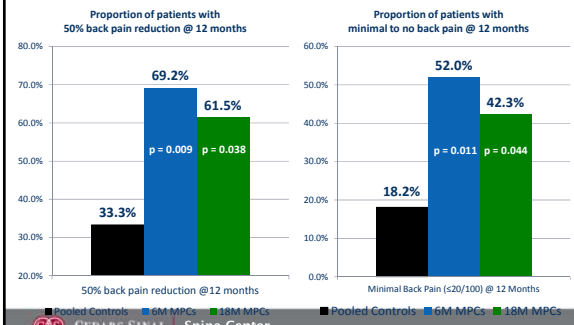
Inclusion Criteria

- DDD with back pain >6 months
- Failed 3 Months Non-Operative Care
- Patients with a modified Pfirrmann score of 3, 4, 5 or 6
- With or without contained disc herniation up to a 3mm protrusion with no radiographic evidence of neurological compression.
- Disc height loss of <30% compared to a normal adjacent disc based upon radiographic evaluation
- VAS Back pain >40
- ODI Score >30

Exclusion Criteria

- Modified Pfirrmann score of 1 & 2 or 7 & 8
- Clinically significant nerve or sacroiliac joint pain.
- Clinically significant facet pain as determined by a diagnostic medial branch block or facet joint injection
- Symptomatic involvement of more than one lumbar disc level.
- Intact disc bulge/protrusion or focal herniation at the symptomatic level(s) > 3 mm or presence of disc extrusion or sequestration
- Discs with full thickness tears with free flowing contrast through the annulus fibrosis
- Lumbar intervertebral foraminal stenosis at the affected level(s) resulting in clinically significant spinal nerve root compression.

MPC groups have a greater proportion of patients with at least a 50% improvement in back pain or minimal/no residual back pain at 12 months relative to controls



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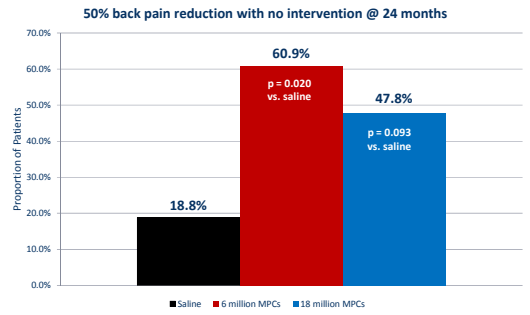
MPC groups have a significantly greater proportion of patients with a 50% pain reduction with no intervention compared to saline @ 24 months



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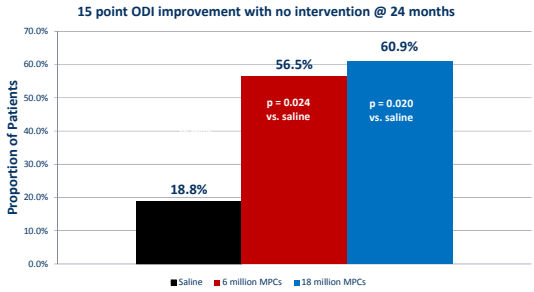
MPC groups have a significantly greater proportion of patients with clinically significant function improvement and no intervention compared to saline @ 24 months



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Missing Link

Evidence Based Efficacy

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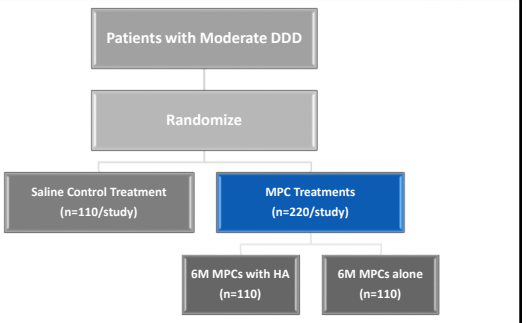
Phase 3 Clinical Study Groups



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Mesoblast Phase III Study

- 60 investigative sites across US and Australia
- 660 subjects
- 2 identical protocols:
  - MSB-DR002
  - MSB-DR003
  - Only MSB-DR003 will undergo interim analysis
- Study period (subject): ~15 months
- Randomization scheme – 1:1:1
  - rexlemestrocel-L + saline
  - rexlemestrocel-L + HA
  - Saline
- First patient screen target date: 05 March 2015
- Last patient screen target date: 09 November 2016

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