Treatment of Degenerative Disc Disease With Allogeneic Mesenchymal Stem Cells: Long-term Follow-up Results

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Degenerative disc disease frequently results in severe low back pain, which represents a public health problem with great economic and quality of life impact. Chronic cases often require surgery, which can lead to biomechanical problems and accelerated degeneration of the adjacent segments.[1,2] Both autologous[3] and allogeneic[4] mesenchymal stromal cell (MSC) treatments have shown feasibility, safety, and strong indications of clinical efficacy 1 year after cell transplantation. Allogeneic cells are logistically more convenient for generalized treatment (see discussion in Noriega et al[4]), and the durability of the effect is essential. We present here the long-term (3.5 ± 0.1 y; mean ± SEM; n = 23) results of our randomized, controlled trial using allogeneic bone marrow-derived MSCs.[4]

We originally randomized 24 patients, 17 men and 7 women, with chronic back pain diagnosed with lumbar disk degeneration (to 1 or 2 discs) and unresponsive to conservative treatments into 2 groups. The mean (±SEM) age was 38 years (±2 y). The further details of the baseline demographics and the inclusion and exclusion criteria are given in Noriega et al.[4] The bone marrow cells were obtained from healthy donors, purified, and expanded for 24–27 days (3 passages) under Good Manufacturing Practice criteria (details in Orozco et al[3] and Noriega et al[4]). The treatment group received the allogeneic bone marrow MSCs as intradisc injections of 25×10^6 cells per segment under local anesthesia. The control group received sham infiltration in the paravertebral musculature with the anesthetic. Clinical outcomes were followed for 1 year, and included evaluation of pain (Visual Analog Scale: 0–100), and disability (Oswestry Disability Index).[5] Disc quality was followed using MRI and quantified according to the Pfirrmann grading (1–5).

Feasibility and safety were confirmed, and indications of clinical efficacy were identified. The MSC-treated patients showed rapid and significant improvements in the algofunctional indices versus the controls. Furthermore, disc degeneration quantified by the Pfirrmann grading improved in the MSC-treated patients and worsened in the controls.[4]

Here, we report the results of the patient follow-up at (mean ± SE; n = 23) 3.5 ± 0.1 years from the original interventions. No serious adverse effects were recorded during this extension period for either treatment or control group. Figure 1A–D summarizes the evolution of the clinical data. For the test group, the early pain improvements and the Oswestry Disability Index improvements during the first year persisted 3.5 years later (Figure 1A and B). The therapeutic efficiency of the MSC treatment was estimated from the pain relief and the disability improvement in the Huskisson plot and was 0.28 at 1 year after the intervention. By 3.5 years, the therapeutic efficiencies increased to 0.60 (pain relief) and 0.71 (disability) (Figure 1C and D). The control patients did

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J.G.-S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. D.C.N., F.A., M.A.M.-F., J.M.M., A.S., and J.G.-S. participated in the conception and design of the study. D.C.N., F.A., and R.H.-R. were primarily responsible for the clinical work. B.T. and I.S.-L. were responsible for the MRI and radiological analysis. M.A., V.G., M.G.-V., and A.S. were responsible for Good Manufacturing Practice cell production. J.G.-S. organized all of the data, conducted the analysis, and wrote the final draft of the article. All authors participated in the analysis, discussion, and interpretation of the data, contributed to the revision of the article, and gave final approval of the version to be published.

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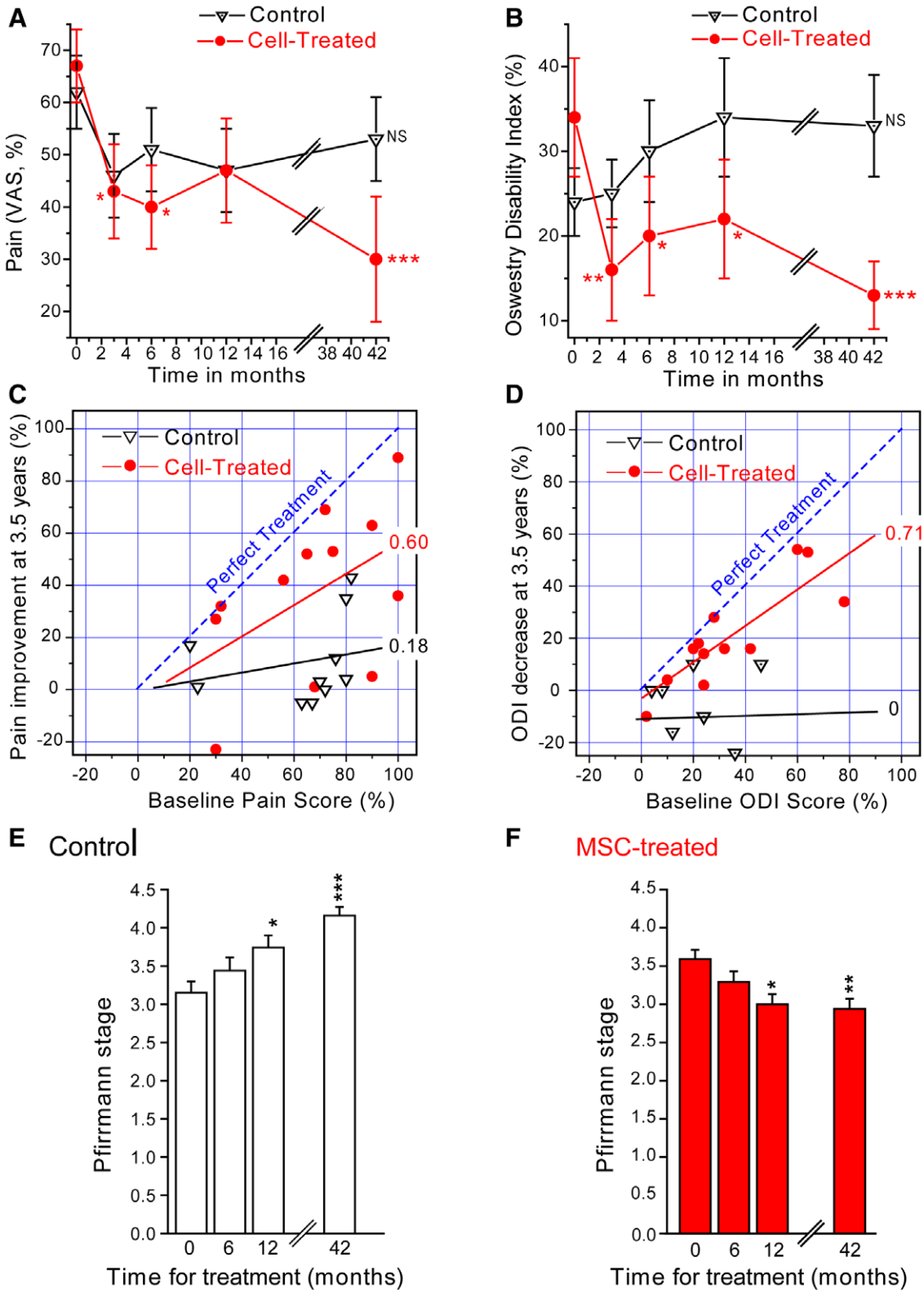

FIGURE 1. Pain, disability, and Pfirrmann grading evolution for the control and mesenchymal stromal cell (MSC)-treated patients. A, Evolution over time of lower back pain measured by a Visual Analog Scale (VAS; expressed as 0%–100%). Data are means ± SD for the control group (inverted triangles) and the MSC-treated group (filled circles). B, Evolution over time of disability measured by the Oswestry Disability Index (ODI) (expressed as 0%–100%).[5] Other details as in (A). C and D, Correlations between improved lower back pain (C, VAS) and disability (D, ODI) and the initial baseline values for each patient,[6] measured at 42 mo from the intervention (3.5 ± 0.1 y; n = 23). The discontinuous blue line shows the slope of 1.0 that represents "perfect treatment" with complete relief of pain (C) and disability (D). The slopes of the lines are given at the right. Other details as in (A). E and F, MRI assessment of nucleus pulposus evolution according to the Pfirrmann grading. The Pfirrmann grading measures affectation (grades 1–5), taking into account the structure of the disc, the distinction of the nucleus pulposus and the annulus fibrous, the signal intensity, and the height of the disc. Data are means ± SE for baseline (0) and 6, 12, and 42 mo (ie, 3.5 y) after the intervention for the control group (E) and the MSC-treated group (F). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ vs baseline (ANOVA, Bonferroni multiple comparisons). NS, not significant.

not show any significant healing at 3.5 years after intervention (efficiency, 0.18 for pain, 0.0 for disability; Figure 1C and D, respectively). Of note, the MSC-treated patients showed 2 distribution patterns: one as a subpopulation of "responders" who lie close to the "perfect treatment" line and the other as a subpopulation of "non responders" with no significant difference from the control patients (Figure 1C and D).

For the structural changes of the affected discs, at the end of the first year of treatment, we reported significant improvements for the MSC treatment, as seen by the decreased Pfirrmann gradings defined from MRI.[4] At 3.5 years, the decreased Pfirrmann grading was maintained in the MSC-treated patients ($P < 0.01$ versus baseline), whereas the control patients showed indication of continued increase in the Pfirrmann grading ($P < 0.001$ versus baseline). Thus, from baseline to 42 months, the Pfirrmann grading significantly increased in the controls by 1.0 (baseline, 3.15; 42 mo, 4.16; Figure 1E), whereas for the MSC-treated patients, there was a significant decrease of >0.6 (baseline, 3.59; 42 mo, 2.94; Figure 1F). This contrasts with the repeatedly reported rapid clearance of MSCs from living tissues.[7] This persistent improvement of the phenotype achieved has been attributed to epigenetic actions of the MSCs.[8,9]

Overall, these long-term data reaffirm that MSCs appear to be a valid alternative for treatment of degenerative disc disease because they can provide effective and durable pain relief together with objective improvements to disc degeneration. This intervention is also simple, although the MSC production process is expensive. The major limitations are the difficulties to generalize the results to large populations, as well as the lack of detailed determination of the optimal dosage of cells. New studies are under way to confirm the durable results reported here in a large series of patients (eg, the pan-European RESPINE clinical trial), and to investigate upgrades to the MSC production protocol, to make the generalization of this MSC therapy possible.

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