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Stroke

1. Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

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Background and Purpose—Preclinical data suggest that cell-based therapies have the potential to improve stroke outcomes.

Methods—Eighteen patients with stable, chronic stroke were enrolled in a 2-year, open-label, single-arm study to evaluate the safety and clinical outcomes of surgical transplantation of modified bone marrow–derived mesenchymal stem cells (SB623).

Results—All patients in the safety population (N=18) experienced at least 1 treatment-emergent adverse event. Six patients experienced 6 serious treatment-emergent adverse events; 2 were probably or definitely related to surgical procedure; none were related to cell treatment. All serious treatment-emergent adverse events resolved without sequelae. There were no dose-limiting toxicities or deaths. Sixteen patients completed 12 months of follow-up at the time of this analysis. Significant improvement from baseline (mean) was reported for: (1) European Stroke Scale: mean increase 6.88 (95% confidence interval, 3.5–10.3; P<0.001), (2) National Institutes of Health Stroke Scale: mean decrease 2.00 (95% confidence interval, −2.7 to −1.3; P<0.001), (3) Fugl-Meyer total score: mean increase 19.20 (95% confidence interval, 11.4–27.0; P<0.001), and (4) Fugl-Meyer motor function total score: mean increase 11.40 (95% confidence interval, 4.6–18.2; P<0.001). No changes were observed in modified Rankin Scale. The area of magnetic resonance T2 fluid-attenuated inversion recovery signal change in the ipsilateral cortex 1 week after implantation significantly correlated with clinical improvement at 12 months (P<0.001 for European Stroke Scale).

Conclusions—In this interim report, SB623 cells were safe and associated with improvement in clinical outcome end points at 12 months.

2. Synergic Effects of Rehabilitation and Intravenous Infusion of Mesenchymal Stem Cells After Stroke in Rats

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Journal of the American Physical Therapy Association 2016

Background Intravenous infusion of mesenchymal stem cells (MSCs) derived from adult bone marrow improves behavioral function in rat stroke models. Rehabilitation therapy through

physical exercise (Ex) also provides therapeutic efficacy for cerebral ischemia.
Objective The purpose of this study was to investigate whether synergic effects of daily rehabilitation and intravenous infusion of MSCs has therapeutic effects after stroke in rats.
Design This was an experimental study.
Methods A permanent middle cerebral artery occlusion (MCAO) was induced by intraluminal vascular occlusion with a microfilament. Four experimental groups were studied: Group 1 (Vehicle only: Vehicle), Group 2 (Vehicle + exercise: Vehicle + Ex), Group 3 (MSCs only: MSCs) and Group 4 (MSCs + Ex: Combined). Rat MSCs were intravenously infused at 6 hours after MCAO and the rats received daily rehabilitation with treadmill running exercise for 20 min. Lesion size was assessed at 1, 14, 35 days using MR imaging. Functional outcome was assessed using the limb placement test.
Results Both combined therapy and MSC infusion reduced lesion volume, induced synaptogenesis and elicited functional improvement compared with the groups without MSC infusion, but the effect was greater in the combined group.
Limitations A limitation of this study is that the results were limited to an animal model and cannot be generalized to humans.
Conclusions These data indicate that the combined therapy of daily rehabilitation and intravenous infusion of MSCs improved functional outcome in a rat MCAO model.

3. Mesenchymal stem cell transplantation attenuates brain injury after neonatal stroke.
van Velthoven CT1, Sheldon RA, Kavelaars A, Derugin N, Vexler ZS, Willemen HL, Maas M, Heijnen CJ, Ferriero DM.
Stroke 2013

BACKGROUND AND PURPOSE:
Brain injury caused by stroke is a frequent cause of perinatal morbidity and mortality with limited therapeutic options. Mesenchymal stem cells (MSC) have been shown to improve outcome after neonatal hypoxic-ischemic brain injury mainly by secretion of growth factors stimulating repair processes. We investigated whether MSC treatment improves recovery after neonatal stroke and whether MSC overexpressing brain-derived neurotrophic factor (MSC-BDNF) further enhances recovery.
METHODS:
We performed 1.5-hour transient middle cerebral artery occlusion in 10-day-old rats. Three days after reperfusion, pups with evidence of injury by diffusion-weighted MRI were treated intranasally with MSC, MSC-BDNF, or vehicle. To determine the effect of MSC treatment, brain damage, sensorimotor function, and cerebral cell proliferation were analyzed.
RESULTS:
Intranasal delivery of MSC- and MSC-BDNF significantly reduced infarct size and gray matter loss in comparison with vehicle-treated rats without any significant difference between MSC- and MSC-BDNF-treatment. Treatment with MSC-BDNF significantly reduced white matter loss with no significant difference between MSC- and MSC-BDNF-treatment. Motor deficits were also improved by MSC treatment when compared with vehicle-treated rats. MSC-BDNF-treatment resulted in an additional significant improvement of motor deficits 14 days after middle cerebral artery occlusion, but there was no significant difference between MSC or MSC-BDNF 28 days after middle cerebral artery occlusion. Furthermore, treatment with either MSC or MSC-BDNF induced long-lasting cell proliferation in the ischemic hemisphere.

CONCLUSIONS:
Intranasal administration of MSC after neonatal stroke is a promising therapy for treatment of neonatal stroke. In this experimental paradigm, MSC- and BNDF-hypersecreting MSC are equally effective in reducing ischemic brain damage.

4. Effects of intravenous administration of allogenic bone marrow- and adipose tissue-derived mesenchymal stem cells on functional recovery and brain repair markers in experimental ischemic stroke.
Gutiérrez-Fernández M, Rodríguez-Frutos B, Ramos-Cejudo J, Teresa Vallejo-Cremades M, Fuentes B, Cerdán S, Díez-Tejedor E.
Stem Cell Research and Therapy 2013

INTRODUCTION:
Stem cell therapy can promote good recovery from stroke. Several studies have demonstrated that mesenchymal stem cells (MSC) are safe and effective. However, more information regarding appropriate cell type is needed from animal model. This study was targeted at analyzing the effects in ischemic stroke of acute intravenous (i.v.) administration of allogenic bone marrow- (BM-MSC) and adipose-derived-stem cells (AD-MSC) on functional evaluation results and brain repair markers.
METHODS:
Allogenic MSC (2 × 106 cells) were administered intravenously 30 minutes after permanent middle cerebral artery occlusion (pMCAO) to rats. Infarct volume and cell migration and implantation were analyzed by magnetic resonance imaging (MRI) and immunohistochemistry. Function was evaluated by the Rogers and rotarod tests, and cell proliferation and cell-death were also determined. Brain repair markers were analyzed by confocal microscopy and confirmed by western blot.
RESULTS:
Compared to infarct group, function had significantly improved at 24 h and continued at 14 d after i.v. administration of either BM-MSC or AD-MSC. No reduction in infarct volume or any migration/implantation of cells into the damaged brain were observed. Nevertheless, cell death was reduced and cellular proliferation significantly increased in both treatment groups with respect to the infarct group. At 14 d after MSC administration vascular endothelial growth factor (VEGF), synaptophysin (SYP), oligodendrocyte (Olig-2) and neurofilament (NF) levels were significantly increased while those of glial fiibrillary acid protein (GFAP) were decreased.
CONCLUSIONS:
i.v. administration of allogenic MSC - whether BM-MSC or AD-MSC, in pMCAO infarct was associated with good functional recovery, and reductions in cell death as well as increases in cellular proliferation, neurogenesis, oligodendrogenesis, synaptogenesis and angiogenesis markers at 14 days post-infarct.

5. Mesenchymal stem cells: therapeutic outlook for stroke.
Honmou O, Onodera R, Sasaki M, Waxman SG, Kocsis JD.
Trends in Molecular Medicine 2012

Adult bone marrow-derived mesenchymal stem cells (MSCs) display a spectrum of functional properties. Transplantation of these cells improves clinical outcome in models of cerebral

ischemia and spinal cord injury via mechanisms that may include replacement of damaged cells, neuroprotective effects, induction of axonal sprouting, and neovascularization. Therapeutic effects have been reported in animal models of stroke after intravenous delivery of MSCs, including those derived from adult human bone marrow. Initial clinical studies on intravenously delivered MSCs have now been completed in human subjects with stroke. Here, we review the reparative and protective properties of transplanted MSCs in stroke models, describe initial human studies on intravenous MSC delivery in stroke, and provide a perspective on prospects for future progress with MSCs.

6. Bone Marrow Mesenchymal Stromal Cell Transplantation: A Neurorestorative Therapy for Stroke
Jieli Chen , Poornima Venkat, Michael Chopp
Cellular Therapy for Stroke and CNS Injuries 2014

A decade long focus on neuroprotection for stroke and neural injury, and its failure to translate into the clinical setting has led to a major shift of focus from neuroprotection to neurorestoration. Neurorestoration involves the remodeling and rekindling of neurovascular plasticity within the central nervous system which drive neurological recovery. Bone marrow-derived mesenchymal stem cell (BMSC) therapy is a promising cell-based neurorestorative therapy for stroke. This chapter provides an update on the use of BMSCs to promote neurorestorative effects in the sub-acute and chronic phases after stroke. The biological processes involved in promoting neurorestorative effects post ischemia are outlined, molecular mechanisms that promote neurogenesis, synaptogenesis, vascular and white matter remodeling, and neurovascular interactions and plasticity are discussed, the involvement of microRNA's in regulating neurorestorative mechanisms is introduced, and an update on clinical trials for BMSC treatment of stroke is presented.

7. Stem cell therapy: a clinical trial of stroke.
Bhasin A, Srivastava MV, Mohanty S, Bhatia R, Kumaran SS, Bose S.
Clinical Neurology and Neurosurgery 2013

BACKGROUND:
The alarming disability burden and a high prevalence rate of stroke in India has encouraged the researchers to develop regenerative therapies to reduce clinical deficits. This study evaluates safety, feasibility and efficacy of autologous mononuclear and mesenchymal cell transplantation in stroke patients evaluated on clinical scores and functional imaging (fMRI and DTI).
METHODS:
Forty (n=40) stroke patients were recruited with the inclusion criteria as: 3 months to 2 years of index event, power of hand muscles of at least 2; Brunnstrom stage: 2-5; conscious and comprehendible. Fugl Meyer (FM), modified Barthel Index (mBI), Medical Research Council (MRC) grade for strength, Ashworth tone scale and functional imaging was used for assessments at baseline, 8 weeks and 24 weeks. 50-60 million cells in 250 ml saline were infused intravenously over 2-3 h.
RESULTS:
The safety test profile was normal with no mortality or cell related adverse reactions in stem cell patients. Among outcome parameters, only modified Barthel Index (mBI) showed statistical

significant improvement ($p<0.05$) in the stem cell group. An increased number of cluster activation in Brodmann areas BA 4, BA 6 was observed post stem cell infusion indicating neural plasticity.

CONCLUSION:

Autologous intravenous stem cell therapy is safe and feasible. Stem cells act as "scaffolds" for neural transplantation and may aid in repair mechanisms in stroke.

8. Transplantation of bone marrow mesenchymal stem cells decreases oxidative stress, apoptosis, and hippocampal damage in brain of a spontaneous stroke model.

Calió ML, Marinho DS, Ko GM, Ribeiro RR, Carbonel AF, Oyama LM, Ormanji M, Guirao TP, Calió PL, Reis LA, Simões Mde J, Lisbôa-Nascimento T, Ferreira AT, Bertoncini CR.
Free Radical Biology and Medicine 2014

Stroke is the most common cause of motor disabilities and is a major cause of mortality worldwide. Adult stem cells have been shown to be effective against neuronal degeneration through mechanisms that include both the recovery of neurotransmitter activity and a decrease in apoptosis and oxidative stress. We chose the lineage stroke-prone spontaneously hypertensive rat (SHRSP) as a model for stem cell therapy. SHRSP rats can develop such severe hypertension that they generally suffer a stroke at approximately 1 year of age. The aim of this study was to evaluate whether mesenchymal stem cells (MSCs) decrease apoptotic death and oxidative stress in existing SHRSP brain tissue. The results of qRT-PCR assays showed higher levels of the antiapoptotic Bcl-2 gene in the MSC-treated animals, compared with untreated. Our study also showed that superoxide, apoptotic cells, and by-products of lipid peroxidation decreased in MSC-treated SHRSP to levels similar those found in the animal controls, Wistar Kyoto rats. In addition, we saw a repair of morphological damage at the hippocampal region after MSC transplantation. These data suggest that MSCs have neuroprotective and antioxidant potential in stroke-prone spontaneously hypertensive rats.