Cell Therapy Trials for Stroke: How to Evaluate Safety and Efficacy

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Stroke: Epidemiology

- 2nd leading cause of death in the world (5.47 million, 2002)
- 1st cause of disability worldwide
- Only treatment: tPA (tissue plasminogen activator) <4.5h
Therapeutical windows

- Acute cytoprotection
- Targeting secondary injury & repair
- Neurorestoration: Intracerebral implants, grafts, and scaffolds

**Multiple targets**
- Immune responses (central/peripheral)
- Repair (neuro-, angio, oligo-genesis)
- Plasticity (reorganization)

- Hours
- Weeks/month
- Cyst; glial scar
Research Report

Treatment with bone marrow mononuclear cells induces functional recovery and decreases neurodegeneration after sensorimotor cortical ischemia in rats

Arthur Giraldi-Guimarães¹, Mafra Rezende-Lima¹, Fernando Pereira Bruno¹, Rosalia Mendez-Otero¹

Figure 1: A standard coronal section identified at the level of the anterior commissure of rat brain that divides the right hemisphere into three subregions (ischemic core [IC], ischemic boundary zone [IBZ], and ventricular zone/subventricular zone [VZ/SVZ]) and eight fields (1, the cortex in IC; 2, the striatum in IC; 3–4, the cortex in IBZ; 5–6, the striatum in IBZ; and 7–8, the striatum in VZ/SVZ) for analyses of response to treatment.
Sources of Cells: Bone Marrow derived stem cells
Bone marrow cell treatment decreases neurodegeneration in the penumbra area

FluoroJade C Neuronal death

Giraldi-Guimaraes et al., Brain Research (2009)
BMMC modulate microglia activation 7 days after ischemia
There is a therapeutic window for treatment of cortical ischemia with bone marrow-derived cells in rats

Functional Evaluation of Forelimb: Cylinder test

de Vasconcelos dos Santos, Brain Research 1306 (2010) 149-158
Mechanism of action of BMSC

- **Transdifferentiation**
- **Fusion**
- **Paracrine effect**
- **Angiogenesis**
- **Neurogenesis** (Neuronal stem cells)

*Microglia*
Conclusion

Cell therapy in stroke- Animal models

- In adult rats subjected to MCA occlusion, different types of **Stem Cells** administered IV or IA decreased the penumbra area and increased functional recovery
- **Bone marrow derived stem cells** (mesenchymal or mononuclear cell fraction) have a beneficial effect in animal models of ischemia ([Giraldi-Guimarães et al., Brain Research, 2009; deVasconcelos dos Santos A. et l., Brain Research, 2010])
Safety and feasibility of autologous bone marrow cell transplantation in patients with ischemic stroke

Gabriel R. de Freitas
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Mauricio Friedrich

Approved by CONEP
ClinicalTrials.gov NCT 00473057
Study design

Ischemic stroke MCA

Acute <10 days IA N=26

Subacute <90 days IA N=6

Subacute <90 days EV N=5

Hospital Procardiaco, Rio de Janeiro
Hospital Universitario/UFRJ, Rio de Janeiro
Hospital São Lucas/PUC, Porto Alegre
Methods

Inclusion criteria:

- Age between 18 and 75
- Ischemic stroke involving the MCA territory (CT/ MRI)
- NIHSS between 4 and 30
- Spontaneous recanalization of the MCA by TCD and/or MRI
Inclusion criteria:

- Age 18 to 75;
- Acute ischemic stroke (≤10 days) in the MCA;
- NIHSS 4 to 30;
- 0.5-10 x 10^6 cells/Kg
- IA

N=26
Periprocedural Evaluation

Continuous EEG monitoring

Continuous TCD monitoring
Results

Friedrich et al., Cell Transplantation, 2012
Migration and homing of BMMNCs in acute stroke

10% of the BMMNCs labeled with 99m-Tc
Intra-arterial Injected Autologous Bone Marrow Mononuclear Cell Distribution by Radioactive Labeling in Acute Ischemic Stroke (D 7)

10% BMMC labeled with 99mTc

Correa et al., 2007,
Clinical Nuclear Medicine • Volume 32, Number 11, November 2007 p 839-41.
Conclusion I

- Intra-arterial injection of autologous BMMC in the MCA is **feasible** and **safe** in acute stroke.

- In **acute** patients BMMCs labeled with Tc migrate to the lesion site.

- Phase II/III studies will be required to evaluate the efficacy of BMMC transplantation in **acute** stroke.
Study design

Ischemic stroke
MCA

- Acute <10 days IA N=26
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Inclusion criteria:

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- Acute ischemic stroke (≤90 days) in the MCA;
- NIHSS 4 to 30;
- 0.5-10 x 10^6 cells/Kg
- IA / EV
99mTc-BMMMC migrate to the ipsilesional hemisphere in subacute patients

Whole Body scan

Planar images

P1 67 days after stroke
P2 82 days after stroke
Early Tissue Distribution of Bone Marrow Mononuclear Cells After Intra-Arterial Delivery in a Patient With Chronic Stroke

Lea Mirian Barbosa da Fonseca, MD, PhD; Valeria Battistella, MD; Gabriel Rodriguez de Freitas, MD, PhD; Bianca Gutifilen, PhD; Regina Coeli dos Santos Goldenberg, PhD; Angelo Maiolino, MD, PhD; Eduardo Wajnberg, MD; Paulo Henrique Rosado de Castro; Rosalia Mendez-Otero, MD, PhD; Charles Andre, MD, PhD

A 24-year-old man with a cerebral infarct within the left middle cerebral artery (MCA) territory was enrolled in a study to assess the safety of autologous bone marrow mononuclear cell (BMMC) transplantation in patients with ischemic stroke (NCT00473057). His National Institutes of Health Stroke Scale score was 7. Computed tomography (Figure 1A) and technetium-99m ethyl cysteinate dimer (99mTc ECD) single photon emission computed tomography (SPECT) (Figures 1B and 2 and Movie I in the online-only Data Supplement) indicated the location of the infarct. Sixty-seven days after onset of symptoms, the patient underwent BMMC transplantation. Bone marrow blood was aspirated under local

Figure 1. A, Computed tomography showing ischemic lesion in the left MCA territory. B, Brain perfusion 99mTc ECD SPECT showing left hypoperfusion. C, 99mTc BMMC brain SPECT revealing accumulation of the BMPCs in the left brain hemisphere 2 hours after cell transplantation.

(Circulation. 2009;120:539-541.)
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Conclusions

• IA or EV injection of autologous BMMC is feasible and safe in acute and subacute stroke.

• In both acute and subacute patients BMMC migrate to the lesion site and can be traced for at least 24 hs.

• Phase II/III studies to assess the efficacy of BMMCs in acute stroke – Approved and funded by PROBITEC (Brazil-Argentina)- 2013

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