The Texas Heart Institute® Journal

International Symposium on Cardiovascular Regenerative Medicine

Repeated Intravenous Administration of Mesenchymal Stromal Cells Produces Cumulative Beneficial Effects in Chronic Ischemic Cardiomyopathy

Xian-Liang Tang, MD; Roberto Bolli, MD

Institute of Molecular Cardiology, University of Louisville, Louisville, Kentucky

Keywords: Adult stem cells; intravenous administration; cardiomyopathy; myocardial infarction; swine

Introduction

Cell therapy is a potentially useful approach to treating heart failure (HF) secondary to chronic ischemic cardiomyopathy (ischemic HF).[1] Despite controversy,[2] the preclinical data in the field of cell therapy are clear: Although transplanted cells do not regenerate cardiomyocytes, preclinical studies have consistently shown that they improve cardiac performance.[1,2] Bone marrow–derived mesenchymal stromal cells (MSCs) are among the most promising cell types in the preclinical arena[1] and for patients with ischemic HF.[3]

The field of cell therapy is evolving rapidly. The fundamental shift has been the recognition that all cell types fail to engraft in the heart and instead work via paracrine mechanisms. This concept has 2 corollaries: (1) because transplanted cells do not persist in the heart for more than a few weeks, giving repeated doses seems logical; and (2) because cells work by releasing factors in the environment, intravenous (IV) therapy may also be effective by enabling systemic release of these factors.

Several considerations provide a rationale for IV cell therapy. First, although a single cell dose may produce some benefit, multiple doses are more likely to be effective[4]; the concept of repeated treatments then inevitably leads to the question of whether cells can be delivered intravenously, because this route would be by far the most practical for administering multiple doses. Second, because it is well established that transplanted cells (including embryonic stem cells) do not engraft, delivery to the heart may not be necessary. Third, because the progressive deterioration in left ventricular (LV) function in HF is caused, at least in part, by persistent systemic inflammation resulting from activation of the immune system, interventions that reduce systemic inflammation may be helpful. Fourth, IV infusion of MSCs exerts systemic anti-inflammatory and immunomodulatory actions. On the basis of these considerations, we sought to determine whether 3 IV administrations of MSCs, performed 30 days apart, would result in cumulative improvement in LV function in rat and swine models of chronic ischemic cardiomyopathy.

Citation: Tang XL, Bolli R. Repeated intravenous administration of mesenchymal stromal cells produces cumulative beneficial effects in chronic ischemic cardiomyopathy. *Tex Heart Inst J*. 2023;50(5):e238244. doi:10.14503/THIJ-23-8244
Corresponding author: Roberto Bolli, MD, Institute of Molecular Cardiology, University of Louisville, 550 S Jackson St, ACB Bldg, 3rd Floor, Louisville, KY 40202 (rbolli@louisville.edu)

Recent Developments

In rats, we found that a single IV infusion of syngeneic MSCs did not produce a significant improvement in LV function, but 3 infusions, 30 days apart, did. We then tested this concept in a preclinical model. Pigs with a 30-day-old myocardial infarction were randomly assigned to 3 groups and received 1 of the following at 5-week intervals: (1) 3 IV doses of vehicle (vehicle group), (2) 1 IV dose of allogeneic bone marrow–derived MSCs and 2 doses of vehicle (single-dose group), or (3) 3 IV doses of MSCs (repeated-doses group). Pigs were euthanized 5 weeks after the third treatment. Echocardiographic studies were performed at baseline (before myocardial infarction), 30 days after myocardial infarction, immediately before the first treatment, 5 weeks after the first treatment, 5 weeks after the second treatment, and 5 weeks after the third treatment. Magnetic resonance imaging (MRI) scans and hemodynamic studies with pressure-volume catheters were performed at before treatment and at 5 weeks after the third treatment. Echocardiographic data showed that LV ejection fraction improved significantly after each of the 3 treatments, both with 1 dose and with 3 doses of MSCs. The MRI and hemodynamic studies showed that ejection fraction after vs before treatment increased significantly compared with vehicle in the repeated-doses group but not in the single-dose group. End-systolic elastance increased significantly compared with vehicle in the single-dose group and, to an even greater extent, in the repeated-doses group. There was a significant reduction in collagen content in the noninfarcted region in the repeated-doses group, indicating an antifibrotic effect of MSCs but not in the single-dose group. Although cardiomyocyte cross-sectional area in the noninfarcted zone was reduced in both treated groups, the decrease was greater with 3 doses. Interestingly, the tissue density of CD68-positive cells (macrophages) in the nonischemic and border zones was increased with 3 doses but not with 1 dose of MSCs, possibly reflecting increased tissue infiltration by reparative macrophages.

Thus, in a porcine model of chronic ischemic cardiomyopathy, we found the following: (1) IV infusion of either 1 or 3 doses of allogeneic bone marrow–derived MSCs improved LV systolic function as assessed by 3 independent methods (MRI, echocardiography, and hemodynamic studies); (2) these salubrious effects were more pronounced after 3 doses than after 1 dose, which supports a cumulative effect of repeated doses, similar to our findings in rats; and (3) 3 doses of MSCs, but not 1 dose, resulted in decreased myocardial fibrosis and hypertrophy and increased macrophage infiltration in the noninfarcted zone.

Taken together, our studies in rats and pigs demonstrate that IV infusions of MSCs are beneficial and have cumulative effects, providing a rationale for clinical trials. Intravenous delivery is simple, inexpensive, and safe and can be performed almost everywhere in almost all patients with HF, even as an outpatient procedure, and is exquisitely suitable for repeated infusions of cells. We propose that the time has come to test this approach in patients.

Abbreviations and Acronyms

HF	heart failure
IV	intravenous
LV	left ventricular
MRI	magnetic resonance imaging
MSC	mesenchymal stromal cell

Article Information

Published: 16 October 2023

Author Contributions: R. Bolli contributed to the design of the research, to overseeing the experiments, to the interpretation of the results, and to the writing of the manuscript. X. L. Tang contributed to the performance of the experiments, to the experimental data collection, to the analysis of the results, and to the manuscript preparation.

Conflict of Interest Disclosure: None.

Funding/Support: NIH P01HL78825.

Section Editor: Emerson Perin, MD, PhD.

Meeting Presentation: Presented at the 3rd Annual International Symposium on Cardiovascular Regenerative Medicine; May 12-13, 2023; Houston, TX.

References

1. Bolli R, Solankhi M, Tang XL, Kahlon A. Cell therapy in patients with heart failure: a comprehensive review and emerging concepts. *Cardiovasc Res.* 2022;118(4):951-976. doi:10.1093/cvr/cvab135
2. Bolli R, Tang XL, Guo Y, Li Q. After the storm: an objective appraisal of the efficacy of c-kit+ cardiac progenitor cells in preclinical models of heart disease. *Can J Physiol Pharmacol.* 2021;99(2):129-139. doi:10.1139/cjpp-2020-0406
3. Banerjee MN, Bolli R and Hare JM. Clinical studies of cell therapy in cardiovascular medicine: recent developments and future directions. *Circ Res.* 2018;123(2):266-287. doi:10.1161/CIRCRESAHA.118.311217
4. Wysoczynski M, Khan A and Bolli R. New paradigms in cell therapy: repeated dosing, intravenous delivery, immunomodulatory actions, and new cell types. *Circ Res.* 2018;123(2):138-158. doi:10.1161/CIRCRESAHA.118.313251