Translation of IGF-1 as a cardioprotection agent: From cells to clinic reality

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Introduction

Loss of cardiac function following myocardial infarction (MI) remains a leading cause of morbidity in the developed world. In the aftermath of MI, complete functional recovery of the heart is still not realized in many patients due to cardiac tissue loss as a result of incomplete salvage of muscle tissue causing deterioration of hemodynamic function and eventual progression to heart failure. In response, regenerative medicine-based approaches have been applied with the goal of preserving or even restoring at-risk tissue ultimately transforming the quality of life for patients with severe ventricular dysfunction and heart failure.

More than a decade of regenerative research has identified new insight into cardiac repair from a mechanistic and translational perspective. Long considered a leading cardiac therapy candidate, circulating endothelial progenitor cells (EPC) have shown promise in existing post-infarction cardiac repair responses reducing infarct size by up to 50%. Early studies from our laboratory identified evidence between the therapeutic benefit elicited from EPC conditioned media versus whole cell delivery suggesting a paracrine therapeutic mechanism. Further studies using cytokine array and functional blocking studies identified insulin-like growth factor-1 (IGF-1) within the EPC conditioned media as being a critical mediator of acute myocardial repair post-MI with respect to cardiomyocyte survival, contractility, and angiogenesis in vivo.

Accordingly, we designed a preclinical study faithfully simulating the timing and physiological scale of the onset of acute myocardial infarction utilizing percutaneous left anterior descending artery occlusion and reperfusion in which we assessed low dose IGF-1 as a separate agent in the preservation of positive heart tissue post-ischemia. We established that a one-time delivery of low dose IGF-1 effects potent acute myocardial salvage, reducing cardiomyocyte cell death, activating survival signaling extending to long-term benefits in MI size, wall structure, and a ~25% improvement in left ventricular ejection fraction underscoring its potential as an adjunctive therapeutic agent.

Subsequently, we initiated a Phase I/II human trial, RESUS-AMNCT01438808, evaluating the safety and efficacy of intravenous delivery of IGF-1 as an adjunctive cardiprotective agent post PCI in patients with ST segment elevation myocardial infarction. With enrollment nearing completion, this study is evaluating global left ventricular ejection fraction (LVEF) measured by quantitative cardiac magnetic resonance imaging as a primary efficacy outcome.

Methods

Figure 1: Preclinical Myocardial Infarction model for therapeutic units or cardioprotective factor. Percutaneous occlusion of the left anterior descending (LAD) artery reproduces myocardial infarction. Subsequent development of ischemic tissue necrosis and hemorrhage results in cell death.

Figure 2: Characterization of Endothelial Progenitor Cells (EPC), Intracellular and Superoxide Anion Detection in Myocardial Ischemia. A: A and B, Statistical analysis of cells positive for adherence, B and C, D, and E, Dihydroxy-benzaldehyde fluorescence in the ischemic region of diaphragm stained by EPC, NBT staining. F, A positive control stained for superoxide anion by EPC. C, A: A and B, Statistical analysis of cells positive for adherence, B and C, Dihydroxy-benzaldehyde fluorescence in the ischemic region of diaphragm stained by EPC, NBT staining. F, A positive control stained for superoxide anion by EPC.

Results

Figure 3: Quantitative results from IGF-1 show equivalence to whole cell in preserving heart function post MI. Changes in preinfarct territory structure and function assessed by MRI in each treatment group baseline to two weeks post MI demonstrates that IGF1 reduces infarct size by up to 50% in all groups. Changes in infarct size expressed as a percentage of infarct size to total area in all groups. B: Changes in infarct cell death measured during necrosis expressed in percentage. C: Changes in infarct cell death measured during necrosis expressed in percentage. D: Changes in infarct cell death measured during necrosis expressed in percentage. E: Changes in infarct cell death measured during necrosis expressed in percentage.

Figure 4: Effect of EPC-conditioned media on left ventricular ejection fraction. A: A phase of preischemic function left ventricular ejection fraction (LVEF) before ischemia. B: A phase of postischemic function left ventricular ejection fraction (LVEF) after ischemia. C: A phase of postischemic function left ventricular ejection fraction (LVEF) after ischemia. D: A phase of postischemic function left ventricular ejection fraction (LVEF) after ischemia. E: A phase of postischemic function left ventricular ejection fraction (LVEF) after ischemia. F: A phase of postischemic function left ventricular ejection fraction (LVEF) after ischemia.

Figure 5: LV-LDH-IGF1 attenuates left ventricular remodeling 2 months post myocardial infarction. A: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). B: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). C: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). D: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). E: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey).

Figure 6: LDH-IGF1 administration reduces infarct size at 24 hours. A: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). B: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). C: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). D: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey). E: Representative RT image and corresponding analysis of left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and LVEF (left ventricular ejection fraction) in untreated controls (black) and IGF1 treated pigs (grey).

Figure 7: A Randomized Trial Evaluating the Safety and Efficacy of a Single Low Dose Intravenous Insulin-Like Growth Factor-1 Following Percutaneous Coronary Intervention for ST-Gadgets Acute Myocardial Infarction. SFI, www.clinicaltrials.gov identifier: NCT01074184.

Summary

Regenerative medicine has as one of its arms, reduction in the excessive morbidity and mortality associated with loss of heart function post infarction. Through cell therapy investigations, we established IGF-1 as a key cytoprotective factor in the endothelial progenitor cell secreteome. Moreover a one-time delivery of low dose IGF-1 effected potent acute myocardial salvage when delivered to the infarcted heart. Subsequently, we initiated a first-in-man trial evaluating the safety and efficacy of ten low doses of IGF-1 as an adjunctive cardioprotective agent post myocardial infarction thus applying a paradigm of investigative regenerative medicine to the clinical arena.

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