BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: Journal of Biomedical Research & Environmental Sciences

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: https://www.jelsciences.com

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: Medicine Group, Biology Group, General, Environmental Sciences

Topics Summation: 133

Issue Regularity: Monthly

Review Process: Double Blind

Time to Publication: 21 Days

Indexing catalog: IndexCopernicus ICV 2022: 88.03 | GoogleScholar | View more

Publication fee catalog: Visit here

DOI: 10.37871 (CrossRef)

Plagiarism detection software: iThenticate

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: SciRes Literature LLC

IndexCopernicus ICV 2022: 83.03

Manuscript should be submitted in Word Document (.doc or .docx) through

Online Submission

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JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
ISSN: 2766-2276
SUBJECT AREA(S): CLINICAL CARDIOLOGY | CLINICAL TRIALS | CARDIOVASCULAR DISEASES
DOI: 10.37871

SHORT COMMUNICATION

Autologous Angiogenic Cell Precursors- A Molecular Strategy for the Treatment of Heart Failure: Response to Biocardia's Cardiamp HF Trial

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Introduction

Stem cell therapy for the treatment of heart failure in patients not adequately responding to optimized heart failure medication is currently being studied in clinical trials, with the hope of improved heart function and quality of life. BioCardia was granted FDA Breakthrough Designation for its Phase III trial of CardiAMP® Cell Therapy for the treatment of Heart Failure with reduced Ejection Fraction (HFrEF). Unfortunately, BioCardia's phase 3 trial one-year follow-up failed to reach its endpoint, which has dampened enthusiasm for HFrEF stem cell treatment. The CardiAMP-HF Trial studied 125 ischemic heart failure patients with reduced ejection fraction enrolled at 18 centers in the United States and Canada. All patients were maintained on heart failure medication, the treatment group receiving a single dose of CardiAMP Cell Therapy - autologous bone marrow cells delivered by transcatheter, intracoronary technique. The primary endpoint of the study - the all-cause of death, including cardiac death equivalents- failed to show any benefit. The treated group reported a 5.6% rate of all-cause death and cardiac death equivalents after one year, compared to 5.3% in the control group. Moreover, nonfatal major adverse cardiac events were similar in the two cohorts, with 16.7% in the treatment group versus 15.8% in the control, and there was no difference between the two groups in the Six-Minute Walk test distance. BioCardia concluded that the current phase III study was unlikely to succeed, given the failure of the bone marrow cell therapy to significantly improve outcomes on any aspect of the composite endpoint of the trial.

However, subgroup analysis of those patients with elevated Brain derived Natriuretic Peptide (BNP) showed decreased mortality and major adverse cardiac and cerebrovascular events, improved quality of life, a modest improvement in left ventricular ejection fraction, and an improvement in the Six Minute Walk Distance. In a not surprising turn, BioCardia has initiated patient enrollment for a CardiAMP HF II

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DOI: 10.37871/jbres2100

Submitted: 01 May 2025

Accepted: 08 May 2025

Published: 12 May 2025

MEDICINE GROUP

CLINICAL CARDIOLOGY | CLINICAL TRIALS | CARDIOVASCULAR DISEASES

VOLUME: 6 ISSUE: 5 - MAY, 2025

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How to cite this article: Henderson FC, Tuchman K, Sarel I. Autologous Angiogenic Cell Precursors- A Molecular Strategy for the Treatment of Heart Failure: Response to Biocardia's Cardiamp HF Trial. J Biomed Res Environ Sci. 2025 May 12; 6(5): 433-438. doi: 10.37871/jbres2100, Article ID: JBRES2100, Available at: https://www.jelsciences.com/articles/jbres2100.pdf

Study. The new study will focus on the subgroup of patients suffering from active heart stress (those with elevated NT-proBNP biomarker). BioCardia's trial illustrates the primary importance of selecting the subpopulation of cardiomyopathy patients likely to respond favorably to stem cell therapy. The Biocardia study showed more significant improvement in patients with elevated BNP biomarkers. BNP occurs in response to increased ventricular wall strain and to volume overload, and elevations of BNP characterize up to 90% of patients with Dilated Cardiomyopathy (DCM).

As the most common form of non-ischemic cardiomyopathy worldwide, DCM may be a more favorable candidate population for stem cell therapy. With an estimated prevalence of 1 in 2500 persons, DCM is defined by dysfunction of the left or both left and right ventricles, with dilation of the ventricular walls. The prognosis is extremely poor. DCM is a leading cause of the need for heart transplantation in adults [1]. Despite improved medical treatment, there is a trend towards worsening of left ventricular function [2]. Systematic reviews have demonstrated beneficial therapeutic effects of adult bone marrow-derived stem cells for non-ischemic DCM, in terms of improved systolic function and mortality [3,4]. Other reviews report improvement of left ventricular ejection fraction, end systolic and end diastolic volume in DCM, but caution that the ultimate clinical implications of these improvements are uncertain [5-7]. There have been no concerns as to the safety of stem cell treatments [8,9].

The histopathology of DCM is a prototypical inflammatory condition, manifesting the full spectrum of immune response. Both resident and recruited inflammatory cells- including macrophages, dendritic cells, granulocytes, B and T cells, and NK cells - release cytokines, including IL-1β, IL-18, IFN-γ, and TNF-β-promoting a remodeling of the extracellular matrix, collagen deposition, impaired contractility, damaged endothelial function and left ventricular enlargement. Cardiomyocyte injury and the immune cascade that follows ischemia reperfusion injury result in the infiltration of inflammatory cell populations, scar formation, fibrosis and a post-procedure death rate of 7-15% [10]. The development of DCM may result from chronic progressive inflammatory response that leads to remodeling of myocardial tissue and fibrosis due to autoimmune disease and viral myocarditis [11].

The important unanswered question in the BioCardia study is whether the molecular biology of the stem cell type is optimal for the specific pathophysiology being treated. There remains a lack of clarity regarding the relative efficacy of cell type, donor origin, or patient selection in terms of the chronicity of ischemia or the type of cardiomyopathy. Specific attributes of the molecular biology of one cell type might *a priori* suggest improved efficacy. Some cell types might be optimal for the treatment of conditions with underlying inflammation, ischemia, and fibrosis.

Decreasing cardiac fibrosis by CXCL8 attraction of NK cells

Angiogenic precursor cells (ACP-01 cells, Hemostemix Corp), are peripheral blood derived angiogenic progenitor cells offering a compelling treatment of inflammatory disorders such as DCM through attraction of Natural Killer (NK) cells (Figure 1). ACP-01 express high levels of CXCL8 [5], which exhibits chemokine activity toward spatially distant NK cells [12]; the CXCR1 and CXCR2 receptors on NK cells are highly specific to the ligand chemokine CXCL8 [13]. NK cells are a part of the innate lymphoid cell (ILC) population. NK cells stifle collagen production in cardiac fibroblasts, and inhibit the assembly of inflammatory cells in the heart [14]. Suppression of NK cells is associated with DCM. When NK cells are depleted, cardiac eosinophil infiltration occurs. NK-derived IFN-γ decreases the deleterious effect of eosinophils on the myocardium by reducing local eotaxin concentrations, and reducing the ability of eosinophils to migrate to the heart. NK cells isolated from healthy human peripheral blood induce the activation and apoptosis of eosinophils, and prevent the accumulation of certain inflammatory populations in the heart. NK cell infiltration into the myocardium is maximal at 7 days after ischemic injury and militates against cardiac fibrosis by limiting collagen formation in cardiac fibroblasts [14,15].

NK cells expressing IFNγ and other mediators create an anti-inflammatory environment, limiting fibrosis through down regulation of eosinophils and other pro-fibrotic cell types. Murine studies have demonstrated reduction in cardiac myocyte apoptosis and collagen formation, and increase in neovascularization due to expansion of NK cells after bone marrow cell transfers to the heart following myocardial infarct [16].

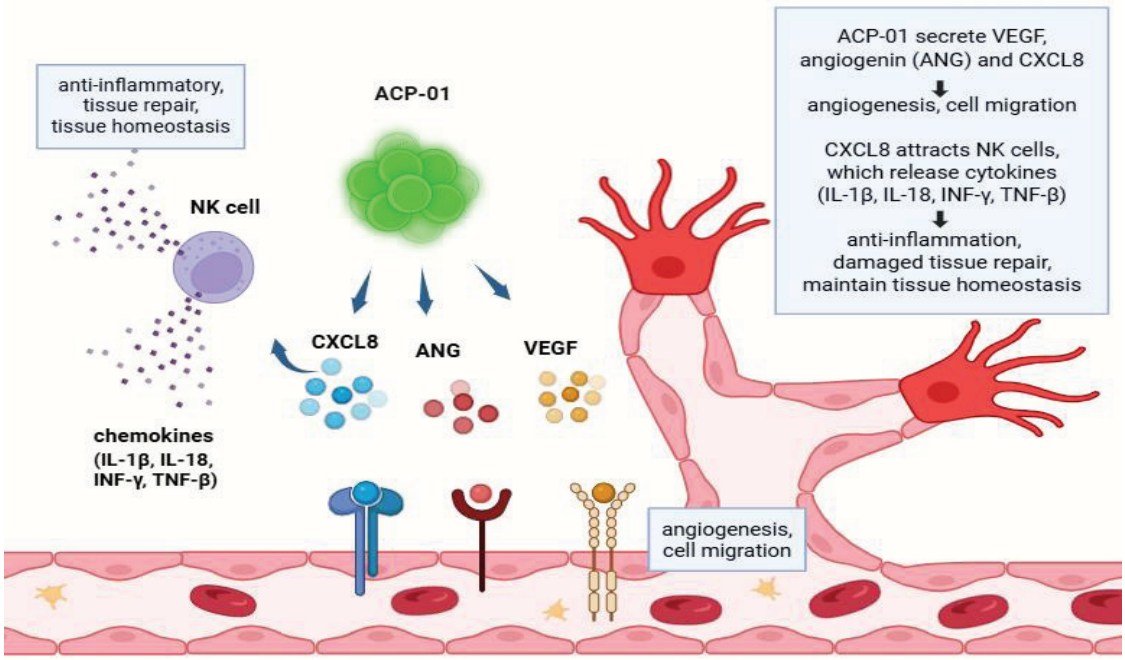

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Figure 1 ACP-01 potentiate healing in heart failure through secretion of tissue regeneration factors such as VEGF, angiogenin and the chemokine IL-8 (CXCL8), promoting cell migration and angiogenesis in ischemic tissues. CXCL8 attracts NK cells, which release anti-inflammatory cytokines and help repair damaged tissues.

DCM may result from a viral infection. Serving in the first line of defense against many intracellular pathogens, NK cells prevent viral replication by detecting and destroying infected resident cells. NK cells suppress inflammation through modulation of immune cell physiology directly through receptor-ligand interactions, and indirectly by cytokine secretion. NK cells are responsible for the initial production of type I interferons, such as IFN-α, IFN-β, and IFN-γ, which initiate the anti-viral inflammatory cascade, and suppress release of T Helper 2 (Th-2) cytokines, decreasing inflammation [11]. NK cell cytokine release may affect alteration of T Helper subtypes, direct contact-mediated lysis of auto-aggressive T cells, and accelerate maturation of monocytes and dendritic cells [17,18]. Through their ability to produce IFNγ and express the transcription factor T-bet, NK cells are important in maintenance of tissue homeostasis [19]. ACP-01 attract NK cells to the sites of repair and thus modulate the immune inflammatory response to injury.

Angiogenesis

The molecular biology of ACP-01 optimizes microcirculation through angiogenesis. ACP-01 are specifically programmed to form endothelial cells and tube-like structures, and to express tissue regeneration factors VEGF and angiogenin, which promote angiogenesis [20]. ACP-01, through expression of high levels of CXCL8, enhance angiogenesis through Ras-MAPK/PI3K activation and the AP-1/NF-kB axis, promoting the proliferation, growth, and viability of vascular endothelial cells [5,21-23].

ACP-01include cells with the CD34 + surface cell marker. CD34+ stromal cells are essential to angiogenesis, participating in cell migration, control and organization of the extracellular matrix, scaffolding, immunomodulation, neurotransmission, control and regulation of other cell types and regeneration [24]. Sprouting angiogenesis requires migration of endothelial cells, alteration of the extracellular matrix, proliferation of endothelial cells and mobilization of the perivascular CD34+Stem Cells. The CD34+ stem cells in ACP-01 are of primary importance in the process of angiogenesis and improved microcirculation [25,26]. However, ACP-01 increased expression of CXCL8 results in mobilization of peripheral CD34+ precursor cells to amplify the angiogenic response [27]. Improved microcirculation minimizes the area of ischemic myocardium, rescuing penumbra and lessening dysfunctional macroscopic remodeling of the surrounding non-ischemic myocardium [28,29].

Autologous cells are not subject to cell-to-cell interactions

As an autologous treatment, ACP-01 are not subject to cell-to-cell interactions [30,31], MHC incompatibilities, or immune rejection from alloreactive antibodies [32]. Moreover, autologous hematopoietic derived stem cells – such as ACP-01- have more prolonged survival than allogeneic cells [33]. The production and sorting method of highly specific hematopoietic progenitor cells, such as autologous ACP-01, results in fewer of the heterogeneous cell populations, which can negatively affect therapeutic results [34]. Fresh autologous cells may be more effective than stored cells [35].

Cell Migration

Finally, ACP-01 minimize ischemic injury to the myocardium through cell migration. Endothelial cell precursors express high levels of CXCR4, which is strongly attracted to chemokines released from injured or ischemic tissue, specifically the CXCL12 chemokine. This CXCR4/CXCL12 axis results in robust migration and embedding of transplanted ACP-01 into injured myocardium [36]. Continuous passage of mesenchymal stem cells during preparation may result in decreased expression of chemokine receptors CXCR2/4; on the other hand, the ACP-01 do not undergo division and multiplication during preparation, the consequence of which is increased demonstration of high expression of CXCR4 receptors [37] and increased homing ability [36]. Embedded ACP-01 support tissue survival through paracrine effect.

Conclusion

Failure of large randomized, multi-institutional studies may be due to the inability to select the appropriate subgroup of patients who are most likely to benefit from stem cell treatment, and from failure to select the optimal stem cell for the specific pathology. Hematopoietic derived stem cells, such as ACP-01, which include the subpopulation of CD34+ cells, are programmed for angiogenesis. Expression of high levels of CXCL8 is of particular importance, moreover, in the attraction of immunomodulatory NK cells, and their ability to inhibit inflammation and stromal fibrosis. These characteristics, and the homing qualities of the ACP-01, contribute to the consistently demonstrated significant improvements of cardiac function in patients treated with ACP-01 [5,38]. Based upon the excellent results previously published on a cohort of patients treated with ACP-01 for cardiomyopathy [5]; Hemostemix is presently planning a phase 1 clinical trial for non-ischemic DCM.

Author Contributions

Professor Fraser Henderson Sr conceived, wrote and edited the manuscript. Kelly Tuchman formatted figure 1 and participated in writing and editing the manuscript. Dr. Ina Sarel participated in writing and editing the manuscript.

Disclosure Statement

Professor Henderson is a practicing, academic neurosurgeon who serves as Chief Medical Officer, and has stock in Hemostemix, Inc. Kelly Tuchman was paid for her work by Hemostemix Inc. Dr. Ina Sarel was the Chief Scientific Officer for Hemostemix Inc. and has stock in the corporation. She is currently head of CMC, Quality and Regulation at NeurExone Biologic, Inc. Potential conflicts of interest have been transparently disclosed , and do not undermine the scientific validity of the work.

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