Use of Granulocyte Colony-Stimulating factor in Management of Cardiovascular Diseases

Marian Salama Youssef Salama, Maha Amin Khattab , Shaimaa Ali Abdelrahman, Abeer Abd Elazeem Mahmoud

Department of Medical Histology and Cell Biology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

Corresponding Author: Marian Salama Youssef Salama

Email: mariansalama2015@gmail.com

Abstract

Background: Heart failure and acute myocardial infarction are conditions that are associated with high morbidity and mortality. Significant dysfunction of the heart muscle can occur as the consequence of end-stage chronic cardiovascular diseases or acute ischemic events that are marked by large infarction area and significant tissue necrosis. Despite the remarkable improvement of conventional treatments, a substantial proportion of patients still develops severe heart failure that can only be resolved by heart transplantation or mechanical device implantation. Therefore, novel approaches based on stem-cell therapy can directly modify the disease process and alter its prognosis. The ability of the stem-cells to modify and repair the injured myocardium is a challenging but intriguing concept that can potentially replace expensive and invasive methods of treatment that are associated with increased risks and significant financial costs. In that sense, granulocyte colony-stimulating factor (G-CSF) seems as an attractive treatment approach. Based on the series of pre-clinical experiments and a limited amount of clinical data, it was demonstrated that G-CSF agents possess the ability to mobilize stem-cells from bone marrow and induce their differentiation into cardiomyocytes or endothelial cells when brought into contact with injured regions of the myocardium.

Keywords: Granulocyte Colony-Stimulating factor, cardiovascular diseases

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1. Introduction

Growth and differentiation of various blood lines from progenitor stem cells is regulated by a group of glycoproteins known as Colony Stimulating Factor (CSF). Four colony stimulating factors, macrophage CSF (M-CSF), granulocyte macrophage CSF (GM-CSF), granulocyte CSF (G-CSF) interferon alpha (INF -α) have been isolated and characterized **(1, 2).**

Granulocyte colony stimulating factor (G-CSF) is formed of 207 amino acids glycoprotein **(3).** The principal sources of G-CSF are monocytes (the most abundant source), macrophages and lymphocytes. In addition, it could be produced by other cells like fibroblasts, astrocytes, neurons, endothelial and bone marrow stromal cells **(4).**

The major target cell of G-CSF is polymorph nuclear leukocytes (PMNL). G-CSF not only promotes neutrophils proliferation but also modulates the function and activity of developing and mature neutrophils **(5).** G-CSF also has trophic effects on different cell types including the neurons **(6).**

G-CSF binds to a single homodimer receptor (G-CSFR) expressed on responsive cells in order to perform its actions. This receptor is part of the cytokine receptor superfamily and hematopoietin receptor superfamily and was

detected in a variety of hemopoietic cells within BM. Binding of G-CSF to its receptors induces intracellular protein tyrosine phosphorylation and triggers multiple signaling mechanisms resulting in transcription of genes important for cell proliferation, differentiation and survival. Studies conducted upon neutrophils showed that only a few receptors are needed to be occupied by G-CSF to elicit a maximal biological response. Patients with hypomorphic mutation in G-CSF receptors usually exhibit marked neutropenia **(7**, **8)**.

In addition, G-CSF induces the mobilization of hematopoietic stem cells (HSCs) from BM toward the peripheral circulation after splitting the links between them and niche where they are stored **(9).** Peripherally, G-CSF influences the survival and chemotaxis of neutrophils as a result of release of arachidonic acid, alkaline phosphatase, myeloperoxidase and superoxide anion. Due to its ability in mobilization of hematopoietic stem cells from the bone marrow into the blood, it can be used not only in hematological malignancies for hematopoietic stem cell transplantation but also as an effective drug for the treatment of chemotherapy-induced neutropenia **(10, 11).**

In female, **Eftekhar et al. (12)** found that G-CSF plays an effective role in pregnancy success not only through improvement of embryo implantation and ovarian functions but also it promotes endometrial thickness. So, G-CSF is considered as a remedy for implantation failure by increase endometrium proliferation and angiogenesis.

Recently, many studies reported that G-CSF has anti-apoptotic and anti-inflammatory effects beside its role in proliferation of the hematopoietic cells.It can protects various types of cells secondary to ischemia-reperfusion (I/R) injury such as muscle cell, neurons **(13).** In Central Nervous System, G-CSF induce neurogenesis to increase neuroplasticity and to counteract apoptosis. **Abdel Mohsen et al. (14) and Keiner et al. (3)** attributed the neurotrophic effect of G-CSF to its ability to prevent oxidatives stress induced by ROS.

Advancements in pharmacological management and evolution of reperfusion techniques, particularly of percutaneous coronary intervention (PCI), have allowed a consistent improvement of long-term prognosis and clinical outcomes among patients that suffer from acute myocardial infarction (AMI) **(15).** However, regardless of the optimal pharmacotherapy and state-of-the-art reperfusion treatment, large randomized controlled trials (RCTs) showed that up to 10% of patients admitted for AMI still develop heart failure (HF) due to extensive myocardial damage and this subsequently results in high yearly rates of rehospitalization due to acute decompensation events and worsening of HF **(16).** End-stage HF almost inevitably ensues in these patients given that cardiomyocyte death from the heart muscle necrosis progresses into dilatation of the ventricular wall thereby significantly incapacitating pump function of the heart **(17).** Furthermore, several pathophysiological mechanisms besides ventricular remodeling and ischemia-related dysfunction are implicated in the failing heart such as increased hemodynamic overload, excessive neurohumoral stimulation, impaired myocyte calcium cycling, accelerated apoptosis, an exorbitant or deficient proliferation of the extracellular matrix and individual genetic predilections ***(18)***

From the epidemiological standpoint, HF still remains as one of the leading causes of morbidity and mortality worldwide and produces significant economic burden in Western societies, with anticipated future rise in incidence due to the improving efficacy of PCI procedures, advances in pharmacological therapy and prolongation of overall human life expectancy **(19).** In patients with advanced and end-stage HF, heart transplantation and implantation of mechanical devices remain as the only therapeutic options, urging for the discovery and implementation of disease-modifying therapies. In respect to this, cell-

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based therapies such as the transplantation of exogenous stem-cells of non-cardiac or cardiac origin into an infarcted region of the heart to induce myocardial regeneration and improve left ventricular (LV) function are under development **(20).** A complementary strategy to this is the stimulation of endogenous regenerative capacity of uninjured cardiac progenitor cells to rebuild myocardium and restore LV function **(20).** Both therapeutic strategies showed favorable effects in improving cardiac function by limiting infarct size expansion and promoting myocardial repair after acute ischemic events through hypothesized paracrine signaling mechanisms **(21),** Although animal studies support the idea that the favorable effects observed from treatment with adult stem-cells are attributable to paracrine effect **(22)**, the exact mechanism of action in humans remains unclear **(23).** Studies performed by Asahara et al. and Kawamoto and colleagues were the first to unveil the trans-differentiation potential of primitive bone marrow cells, namely the potential of bone marrow-derived stem cells (BMDSCs) to differentiate into different specialized cells like cardiomyocytes, endothelial cells, and smooth muscle cells. The first study that assessed the feasibility of these cells in a man showed that administration of intracoronary autologous bone marrow cells to a 46-year-old man after primary PCI for an anterior AMI was successful **(24).** This intracoronary injection of bone marrow stem-cells was associated with a significant improvement of LV function.

Based on this encouraging result, several research groups worldwide tried to regenerate myocardium in animals post-AMI using BMDSCs and achieved amelioration of cardiac function **(25).** In particular, a study performed in the setting of experimentally induced AMI in rats showed that animals treated with granulocyte colony-stimulating factor (G-CSF) showed a dramatic and significant increase in survival in comparison to animals that did not receive G-CSF treatment **(26).**

G-CSF (also known as colony-stimulating factor 3–CSF 3) is a haematopoetic growth factor that can mobilize cells from the bone marrow to the peripheral blood and given that some of these cells are putative stem or progenitor cells it was hypothesized that this treatment strategy might help in improving myocardial perfusion, neovascularization and regeneration of the damaged myocardium in humans**,** However, due to the limited number and small sizes of conducted RCTs, the beneficial effects of stem-cell therapies in AMI patients and patients with chronic ischemic heart disease and congestive HF remain unclear **(20).** A recent sequential analysis of RCTs that examined administration of autologous BMDSCs to patients with AMI or HF showed that the cell-based treatment appeared to be associated with a lower risk of mortality and hospitalization for HF, however, with an unclear effect of this therapy in patients with AMI **(27).** It is clear that substantial future efforts are necessary to elucidate the true effect size and clinical benefit of stem-cell therapy use in human myocardial disease. The aim of this review is to focus on G-CSF agents, their pre-clinical results, and clinical applications/perspectives in the treatment of dysfunctional myocardium, either in the setting of chronic end-stage HF or cardiac dysfunction induced by the severe AMI. Authors will also share some of their own initial clinical experiences with G-CSF therapy.

The pharmacokinetics of G-CSF agents The peak serum concentrations of glycosylated recombinant human G-CSF (rHuG-CSF) immediately after intravenous (i.v.) infusion or after subcutaneous (s.c.) injection, were doseand time- dependent **(28).** Maximum serum concentrations of lenograstim were higher when used in i.v. form, compared to s.c. administration and were attained sooner . The rise in absolute neutrophil counts (ANC) were achieved in a dose-dependent manner with both routes of lenograstim administration, however, more prolonged rises and higher ANC peaks were attained following subcutaneous injection. Similarly, elimination half-lives were longer after

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s.c. injection in comparison to i.v. infusion (2.3-3.3 vs. 0.8-1.2 h, respectively). rHuG-CSF is cleared from the plasma through renal filtration and neutrophil-mediated degradation, showing that increased neutrophil levels are associated with increased clearance of G-CSF **(29).**

Efficacy of G-CSF agents in pre-clinical models of cardiovascular disease

The principal idea behind the clinical use of the rHuG-CSF agents lies in their potential to improve myocardial function and perfusion noninvasively through mobilization of stem-cells from bone marrow into peripheral blood **(30).** In the seminal pre-clinical experiment by Orlic et al., the cardiac repair was characterized by a band of newly-formed myocardium that occupied most of the area affected by ligation-induced AMI, from the border zone to inside of the injured region and from the endocardium to the epicardium of the left ventricular free wall. In untreated mice, instead, there was not any myocardial replacement and a scar tissue was formed. Myocardial regeneration had the effect of attenuating cavity dilatation and mural thinning during the evolution of the infarcted heart in vivo and of improving ventricular performance. At this point, myocardial regeneration seemed like a plausible concept to be translated into clinical arena. A further study by Fukuhara and colleagues demonstrated that G-CSF successfully promoted bone marrow cells to migrate into infarcted mice heart and differentiate into cardiomyocytes **(31).** Later, the preliminary studies performed in humans showed that intracoronary infusion of autologous progenitor cells is a feasible and safe strategy able to beneficially affect post-infarction remodeling processes in the myocardial tissue **(32).**

Translational and clinical applications of G-CSF therapy in cardiovascular disease

In 2001, Shintani and colleagues **(33).** demonstrated that endothelial progenitor cells and their putative precursors, CD34+ cells, were mobilized in the peripheral blood during the acute 10 ischemic event in humans, peaking on day 7, however, concentrations of these cells remained unchanged in the control group. This finding suggested that AMI likely stimulated bone marrow leading to the mobilization of CD34+ cells **(33). Leone et al. (34).** further expanded this concept showing that AMI enhanced spontaneous mobilization of BMDSC's in the peripheral blood, particularly in groups of patients on statin therapy and after PCI, and this mobilization significantly correlated with the global and regional improvement of LV function **(34).** Moreover, this spontaneous mobilization of CD34+ cells significantly correlated to endogenous G-CSF levels in the peripheral blood. Taken together, these two studies supported the concept that pharmacological administration of G-CSF might be a suitable non-invasive method for the regeneration of myocardial tissue and recovery of contractile function after AMI, thus creating a rationale for the subsequent RIGENERA study. A subcutaneous administration of G-CSF is an attractive therapeutic option since it does not require repeated coronary catheterizations and ex vivo cell purification and expansion.

Later, most of the trial analyses evaluated the therapeutic effect on mortality and left ventricular ejection fraction (LVEF) after the subcutaneous administration of G-CSF through a daily dose of 2.5, 5 or 10 μg/kg for four to six days as treatment for AMI, however the numbers of recruited patients were low and the yielded results disparate **(35).** In a study by Ripa and colleagues, bone marrow stem-cell mobilization with subcutaneous G-CSF was safe but did not lead to further improvement in LV function in patients suffering STEMI compared with the recovery observed in the placebo group. In line with this, results from CAPITAL STEM MI randomized trial showed that in patients with moderate left ventricular dysfunction following anterior-wall AMI, treatment with G-CSF was associated with a lower LVEF at 6-month followup and smaller LVEF increase from baseline when compared to placebo, as assessed by 11 radionuclide angiographies **(36).** In terms of safety concerns, G-CSF treatment exhibited similar safety profile relative to placebo and showed a comparable risk of major adverse cardiac events (MACE).

Similarly, no conclusive results on therapy benefit were obtained in patients with STEMI that were treated with subcutaneous G-CSF added to standards of care **(37).**

Finally, relevant meta-analyses pooled the data of the abovementioned trials on G-CSF use thus providing us with a useful overview of this method and stressing the evident problem of a low number of patients enrolled in the trials. The pooled analyses generally conclude that G-CSF therapy was safe and well-tolerated, however, in terms of clinical efficacy, it did not seem to improve the LV function nor to reduce the mortality **(38).** In contrast to this, some other meta-analyses concluded that G-CSF treatment was associated with a significant improvement of the LVEF in patients with AMI **(39, 40).** summarizes the main clinical studies with G-CSF in the setting of AMI.

Stem-cell therapy is an exciting area of cardiovascular research that demonstrated a good safety profile, however, a standardization of experimental treatment modalities along with 16 careful clinical trial design are the absolute requirements for the determination of true effects of this therapeutic approach. Current clinical evidence supporting the benefit of stem-cell treatments in the acute and chronic setting are limited and inconclusive. Furthermore, studies that evaluated the use of G-CSF in myocardial repair have also shown mixed results when it comes to clinical efficacy. However, since the use of G-CSF is a stem-cell-free therapeutic approach, the idea of mobilization of endogenous stem-cells from bone marrow to ameliorate myocardial injury is an attractive concept worth of future undertakings, especially in the light of feasibility and acceptable cost/benefit relationship. Therefore, new and upcoming trials with strictly defined hard end-points will hopefully provide us with the answers to some of the fundamental questions in this field of cardiovascular science. Some of these questions are can the treatments with GCSF agents and stem-cells significantly decrease mortality and re-hospitalization events among patients with significant myocardial injury and, even more importantly, what is the potency of these treatments to act in a disease-modifying fashion thus directly altering the prognosis of the disease **(39, 40).**

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