G-CSF in acute myocardial infarction - Experimental and clinical findings

Akut miyokard infarktüsünde G-CSF - Deneysel ve klinik bulgular

Hüseyin İnce, Michael Petzsch, Tim C. Rehders, Simone Dunkelmann, Christoph A. Nienaber*

From the Department of Medicine, Divisions of Cardiology and *Nuclear Medicine at the University Hospital Rostock, Rostock School of Medicine, Rostock, Germany

ABSTRACT

Early data from clinical studies suggest that intracoronary injection of autologous progenitor cells may beneficially affect postinfarction remodeling and perfusion. Beyond intracoronary infusion of autologous bone marrow mononuclear CD34+ cells (MNCCD34+), mobilization of stem cells by G-CSF has recently attracted attention because of various advantages such as the noninvasive nature of MNCCD34+ mobilization by subcutaneous injections. It is the aim of the present work to give an overview about the current experimental and clinical findings of G-CSF treatment in acute myocardial infarction. *(Anadolu Kardiyol Derg 2006; 6: 261-3)*

Key words: G-CSF, myocardial infarction, stem cells

ÖZET

Önceki çalışmalarda otolog progenitör hücrelerin intrakoroner enjeksiyonun infarktüs sonrası yeniden yapılandırmayı (remodeling) ve perfüzyonu yararlı yönde etkilediklerini belirtilmiştir. Kemik iliğinin otolog mononükleer CD34+ hücrelerin (MNCCD34+) intrakoroner infüzyonun ötesinde, kök hücrelerin G-CSF aracılığı ile mobilizasyonu son zamanlarda noninvazif subkutan enjeksiyonlu MNCCD34+ mobilizasyonu gibi farklı avantajlar nedeni ile dikkati üzerine çekmiştir. Bu çalışmanın amacı akut infarktüsünde G-CSF tedavisinin güncel deneysel ve klinik bulguları gözden geçirmektir. *(Anadolu Kardiyol Derg 2006; 6: 261-3)*

Anahtar kelimeler: G-CSF, miyokard infarktüsü, kök hücreler

Currently, no medication or procedure used clinically, except for cardiac transplantation, has shown efficacy in replacing myocardial scar with functioning contractile tissue. Given the major morbidity and mortality associated with myocardial infarction and subsequent heart failure, recently new generative approaches have been introduced to address the issue of cardiac repair, especially since the dogma of the heart as a post-mitotic organ had recently been challenged by the observation that subpopulation of cardiomyocytes may re-enter the cell cycle and undergo nuclear mitotic division in the infarcted human heart (1-5). Repair of infarcted myocardium has been demonstrated in experimental models of acute myocardial infarction (AMI), with both improved myocardial function and survival, following local administration of bone marrow-derived stem cells (BMSC) (5-8). Recent studies however, failed to find evidence of transdifferentiation of BMSC into cardiomyocyte (9), although intracoronary injection of autologous progenitor cells may beneficially affect postinfarction remodeling and perfusion (10-13).

Beyond intracoronary infusion of autologous bone marrow mononuclear CD34+ cells (MNCCD34+), mobilization of stem cells by granulocyte colony-simulating factor (G-CSF) has recently attracted attention because of advantages such as the noninvasive nature of MNCCD34+ mobilization by subcutaneous injections; moreover, bone marrow aspiration and preparation is not required (potentially difficult in acute patients), and repeat catheterization with intracoronary infusion is avoided. Finally, exposure of post-ischemic injured myocardium to mobilized MNCCD34+ and leukocytes is sustained over the susceptible first week at concentrations markedly exceeding natural cell mobilization, as recently shown in the setting of human studies on myocardial infarction (14).

It is the aim of the present work to summarize the current experimental and clinical findings of G-CSF treatment in acute myocardial infarction.

Experimental findings

In a myocardial infarction model of mice cytokine-induced cardiac repair decreased mortality by 68%, infarct size by 40%, cavity remodeling by 26%, and diastolic stress by 70%, respectively; left ventricular ejection fraction (LVEF) and hemodynamics improved significantly as a consequence of 15 x 10^6 new myocytes connected with arterioles and capillaries to the circulation of unaffected myocardium (7). Similarly, human MNCCD34+ mobilized by G-CSF led to stem cell population exclusively in injured myocardium two days after intravenous injection in rat; at 15 we-

Address for Correspondence: Hüseyin İnce, MD, Division of Cardiology University Hospital Rostock Rostock School of Medicine Ernst-Heydemann-Str. 6 18057 Rostock, Germany Tel.: +49 0381 494 77 00 Fax: +49 0381 494 77 02 E-mail: hueseyin.ince@med.uni-rostock.de

eks new blood vessel formation in the infarct bed and proliferation of preexisting vasculature were observed (7). Moreover, apoptotic cells and infarct size were reduced from 36 to 12 percent with corresponding enhancement of cardiac output. Although both studies suggested beneficial impact of G-CSF to prevent remodeling cytokine treatment was either started before infarction (6) or given in a non-reperfusion setting; both studies are unlikely to reflect the reperfusion scenario in humans. However, recent experimental findings in an occlusion-reperfusion experiment (20) with G-CSF after infarction in rabbits increased LVEF and decreased remodeling at long-term. Minatoguchi et al. (15) could demonstrate in this experimental reperfusion setting that beneficial effect may be derived from G-CSF induced mobilization of leukocytes that are known to play an important role for myocardial repair by regulating phagocytosis of necrotic tissue, fibroblast proliferation and angiogenesis. Moreover, there is evidence of a G-CSF dependent protection of cultured cardiomyocytes from apoptotic cell death through upregulation of Bcl 2 and Bcl xL expression via the G-CSF receptor and the Jak Stat pathway. In vivo experiments have shown the G-CSF led to upregulation of G-CSF receptor and activation of the Stat 3 pathway, thereby preventing both cardiomyocytes apoptosis and remodeling after myocardial infarction (16). Similar results could be demonstrated with G-CSF in experimental stroke models (17, 18).

Recent preliminary data from the MAGIC-trial indicated that G-CSF treatment in patients with acute myocardial infarction could aggravate in-stent restenosis rate (19). Moreover, there is no animal model in which coronary arteries have multiple unstable coronary plaques like in patients with acute myocardial infarction. Theoretically, these plaques might be destabilized by an increased number of circulating leukocytes after G-CSF administration. An elevated white cell count has been suspected to predict an adverse prognosis in acute myocardial infarction (20).

Conversely, there is growing evidence that G-CSF pretreatment as a strategy to stimulate the mobilization of MNCCD34+ accelerates the rate of reendothelialization and inhibits neointimal thickening in balloon-injured carotid arteries in an experimental setting (21). Similarly G-CSF has been shown to enhance endothelialization of small-caliber prosthetic grafts (22, 23). Moreover, in a model of apolipoprotein E deficient mice G-CSF was shown to even reduce atherosclerotic deposits and coronary lesions by lowering LDL cholesterol, and decreasing plaque burden (24).

Clinical findings

Early data from clinical studies suggest that intracoronary injection of autologous progenitor cells may beneficially affect postinfarction remodeling and perfusion (10-13). In contrast to intracoronary infusion of autologous bone marrow mononuclear CD34+ cells (MNCCD34+) mobilization by G-CSF differs in various ways: first, MNCCD34+ mobilization is noninvasive and requires only subcutaneous injections; second, bone marrow aspiration and preparation is not required (potentially difficult in acute patients); third, repeat catheterization with intracoronary infusion is avoided; fourth, exposure to both G-CSF and to mobilized MNCCD34+ begins early after reperfusion in the susceptible phase (25,26); and fifth, exposure of post-ischemic injured myocardium to mobilized MNCCD34+ is sustained over 1 week at concentrations markedly exceeding natural cell mobilization in acute infarction. Whereas intracoronary delivery was enacted as early as 5-9 days (11) or 4.3±1.5 days after onset of necrosis (10), G-CSF induced liberation of MNCCD34+ was initiated within 89 minutes after percutaneous coronary intervention (PCI) in the FIRSTLINE-AMI study trial (15). Yet, Strauer et al delivered only $5.9x10^5$ CD34+ cells (9, 10), while Schachinger et al infused $7.35±7.31x10^6$ CD34/CD45+ cells per patient (11). Assuming an average blood flow of 0.8ml/min/g, 100 grams of injured myocardium were exposed to approximately $2.8x10^{10}$ MNCCD34+ with G-CSF stimulation over 8 days in FIRSTLINE-AMI (27).

An increase of circulating MNCCD34+ after AMI is a well documented phenomenon (25,26) potentially influencing left ventricular function in the post-infarction setting (28) and in congestive heart failure (29). Moreover, there is recent evidence for significant correlation between spontaneous mobilization of MNCCD34+ and endogenous G-CSF in patients with AMI (30). Furthermore, G-CSF is synthesized and released from the heart in the early phase of acute myocardial infarction (31).

Safety and feasibility of G-CSF in acute myocardial infarction has been established by our group (27) and findings are in line with those of Jorgensen et al. (32), Valgimigli et al. (33), Kuethe et al. (34) and Suarez de Lezo et al. (35). Considering those encouraging findings, the application of G-CSF could be a non-invasive option to ameliorate post-infarction remodeling; major concerns, however, have been raised about the safety of G-CSF-treatment in acute myocardial infarction due to the unexpected high in-stent restenosis rate in MAGIC (19). The controversial impact of G CSF with (n=7) or without additional cell infusion (n=3) on in-stent restenosis, however, was deduced from only 10 patients with angiographic follow-up and should be interpreted with caution in the light of recent human studies with no increased risk of in-stent restenosis after G-CSF treatment (27,32-35). The findings of Kang et al could be related to the fact that G-CSF was given for 4 consecutive days prior to PCI. One may speculate that at the time of stent implantation the number of circulating cells of the haematopoietic cell lineage was high, which may in turn be directly related to the degree of neointima formation (36).

Treatment by G-CSF after reperfusion of infarcted myocardium could offer a pragmatic concept of potential myocardial regeneration, which warrants further investigation of developmental potential of stem cells, longer follow-up surveillance and the scrutiny of multicenter, placebo-controlled trials.

References

1. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. Circulation. 2000; 102: IV14-IV23.
2. Pfeffer MA. Left ventricular remodelling after acute myocardial infarction. Annu Rev Med. 1995; 46: 455-66.
3. Beltrami AP, Urbanek K, Kajstura J, Yan SM, Finato N, Bussani R, et al. Evidence that human cardiac myocytes divide after myocardial infarction. N Engl J Med 201; 344: 1750-7.
4. Quaini F, Urbanek K, Beltrami AP, Finato N, Beltrami CA, Nadal-Ginard B, et al. Chimerism of the transplanted heart. N Engl J Med 2002; 346: 5-15.
5. Deb A, Wang S, Skelding KA, Miller D, Simper D, Caplice NM. et al. Bone marrow-derived cardiomyocytes are present in adult human heart. Circulation 2003;107:1245-7.
6. Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F, et al. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Natl Acad Sci U S A 2001; 98: 10344-9.
7. Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, et al.

Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodelling and improves cardiac function. Nat Med 2001; 7: 430-6.
8. Orlic D, Kajstura J, Chimenti S, Jakoniuk I, Anderson SM, Li B, et al. Bone marrow cells regenerate infarcted myocardium. Nature 2001; 410: 701-5.
9. Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature 2004; 428: 664-8.
10. Strauer BE, Brehm M, Zeus T, Kostering M, Hernandez A, Sorg RV, et al. Repair of infarcted myocardium by autologous intracoronary mononuclear bone marrow cell transplantation in humans. Circulation 2002; 106: 1913-8.
11. Schachinger V, Assmus B, Britten MB, Honold J, Lehmann R, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. J Am Coll Cardiol 2004; 44: 1690-9.
12. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomized controlled clinical trial. Lancet 2004; 364: 141-8.13. Fernandez-Aviles F, San Roman JA, Garcia-Frade J, Fernandez ME, Penarrubia MJ, de la Fuente L, et al. Experimental and clinical regenerative capability of human bone marrow cells after myocardial infarction. Circ Res 2004; 95: 742-8.
14. Ince H, Petzsch M, Kleine HD, Schmidt H, Rehders T, Körber T, et al. Preservation from left ventricular remodeling by front-integrated revascularization and stem cell liberation in evolving acute myocardial infarction using granulocyte colony stimulating factor (FIRSTLINE-AMI). Circulation 2005; 112: 3097-106.
15. Minatoguchi S, Takemura G, Chen XH, Wang N, Uno Y, Koda M, et al. Acceleration of the healing process and myocardial regeneration may be important as a mechanism of improvement of cardiac function and remodelling by postinfarction granulocyte colony-stimulating factor treatment. Circulation 2004; 109: 2572-80.
16. Harada M, Qin Y, Takano H, Minamino T, Zou Y, Toko H, et al. G-CSF prevents cardiac remodeling after myocardial infarction by activating the Jak-Stat pathway in cardiomyocytes. Nat Med 2005; 11: 305-11.
17. Shyu WC, Lin SZ, Yang HI, Tzeng YS, Pang CY, Yen PS, et al. Functional recovery of stroke rats induced by granulocyte colony-stimulating factor stimulated stem cells. Circulation 2004; 110: 1847-54.
18. Schneider A, Krüger C, Steigleder T, Weber D, Pitzer C, Laage R, et al. The hematopoietic factor G-CSF is a neuronal ligand that counteracts programmed cell death and drives neurogenesis. J Clin Invest 2005; 115: 2083-98.
19. Kang HJ, Kim HS, Zhang SY, Park KW, Cho HJ, Koo BK, et al. Effects of intracoronary infusion of peripheral blood stem-cells mobilized with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomized clinical trial. Lancet2004; 363: 751-56.
20. Barron HV, Cannon CP, Murphy SA, Braunwald E, Gibson CM. Association between white blood cell count, epicardial blood flow, myocardial perfusion, and clinical outcomes in the setting of acute myocardial infarction: a thrombolysis in myocardial infarction 10 substudy. Circulation 2000; 102: 2329-34.
21. Kong D, Melo LG, Gnecchi M, Zhang L, Mostoslavsky G, Liew C, et al. Cytokine-induced mobilization of circulating endothelial progenitor cells enhances repair of injured arteries. Circulation 2004; 110: 2039-46.
22. Bhattacharya V, McSweeney PA, Shi Q, Bruno B, Ishida A, Nash R, et al. Administration of granulocyte colony-stimulating factor enhances endothelialization and microvessel formation in small caliber synthetic vascular grafts. J Vasc Surg 2000; 32: 116-23.
23. Shi Q, Bhattacharya V, Hong-De Wu M, Sauvage LR. Utilizing granulocyte colony-stimulating factor to enhance vascular graft endothelialization from circulating blood cells. Ann Vasc Surg 2002; 16: 314-20.
24. Guo S, Doherty TM, Espinoza C, Wang X, Espinoza A, Makkar R, et al. Effects of G-CSF on serum cholesterol and development of atherosclerotic plaque in apolipoprotein E-deficient mice. Circulation 2004; 110 (17 Suppl III): III-89.
25. Shintani S, Murohara T, Ikeda H, Ueno T, Honma T, Katoh A, et al. Mobilization of endothelial progenitor cells in patients with acute myocardial infarction. Circulation 2001; 103: 2776-9.
26. Wojakowski W, Tendera M, Michalowska A, Majka M, Kucia M, Maslankiewicz K, et al. Mobilization of CD34/CXCR4+, CD34/CD117+, c-met+ stem cells, and mononuclear cells expressing early cardiac, muscle, and endothelial markers into peripheral blood in patients with acute myocardial infarction. Circulation 2004; 110: 3213-20.
27. Ince H, Petzsch M, Kleine HD, Eckard H, Rehders T, Burska D, et al. Prevention of left ventricular remodelling with G-CSF after acute myocardial infarction: Final one-year results of the FIRSTLINE-AMI trial (Front-integrated revascularization and stem cell liberation in evolving acute myocardial infarction by granulocyte colony-stimulating factor). Circulation 2005; 112: I73-80.
28. Leone AM, Rutella S, Bonanno G, Abbate A, Rebuzzi AG, Giovannini S, et al. Mobilization of bone marrow derived stem cells after myocardial infarction and left ventricular function. Eur Heart J 2005; 26: 1196-204.
29. Valgimigli M, Rigolin GM, Fucili A, Porta MD, Soukhomovskaia O, Malagutti P, et al. CD34+ and endothelial progenitor cells in patients with various degrees of congestive heart failure. Circulation 2004; 110: 1209-12.
30. Leone AM, Rutella S, Bonanno G, Contemi AM, de Ritis DG, Giannico MB, et al. Endogenous G-CSF and CD34+ cell mobilization after acute myocardial infarction. Int J Cardiol 2005 (Epub ahead of print).
31. Fujiwara T, Kameda K, Abe N, Matsunaga T, Okumura K. Granulocyte colony-simulating factor (G-CSF) is synthesized and released from the heart in the early phase of acute myocardial infarction. Circulation 2004; 110 (17 Suppl III):III-250.
32. Jorgensen E, Ripa RS, Helqvist S, Wang Y, Hans Erik Johnsen HE, Grande P, et al. In-stent neo-intimal hyperplasia after stem cell mobilization by granulocyte-colony stimulating factor. Preliminary intracoronary ultrasound results from a double-blind randomized placebo-controlled study of patients treated with percutaneous coronary intervention for ST-elevation myocardial infarction (STEMMI Trial). Int J Cardiol 2005 (Epub ahead of print).
33. Valgimigli M, Rigolin GM, Cittanti C, Malagutti P, Curello S, Percoco G, et al. Use of granulocyte-colony stimulating factor during acute myocardial infarction to enhance bone marrow stem cell mobilization in humans: clinical and angiographic safety profile. Eur Heart J 2005; 18: 1838-45. .
34. Kuethe F, Figulla HR, Herzau M, Voth M, Fritzenwanger M, Opfermann T, et al. Treatment with granulocyte colony-stimulating factor for mobilization of bone marrow cells in patients with acute myocardial infarction. Am Heart J 2005; 150: 115.
35. Suarez de Lezo J, Torres A, Herrera I, Pan M, Romero M, Pavlovic D, et al. Effects of stem-cell mobilization with recombinant human granulocyte colony stimulating factor in patients with percutaneously revascularized acute anterior myocardial infarction. Rev Esp Cardiol 2005; 58: 238-40.
36. Fukuda D, Shimada K, Tanaka A, Kawarabayashi T, Yoshiyama M, Zoshikawa J. Circulating monocytes and in-stent neointima after coronary stent implantation. J Am Coll Cardiol 2004; 43: 18-23.