Published in final edited form as:
J Am Coll Cardiol. 2008 April 15; 51(15): 1438–1439. doi:10.1016/j.jacc.2008.01.017.

An Imperfect Syllogism:

Granulocyte Colony-Stimulating Factor Mobilization and Cardiac Regeneration*

Samuel C. Dudley Jr, MD, PhD, FACC[†,‡] and **David Simpson, BS**[†]

[†]Division of Cardiology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois

[‡]Jesse Brown VA Medical Center, Chicago, Illinois

Abstract

Despite significant progress in pharmaceuticals and medical technology, heart failure remains a major worldwide problem. Most often, heart failure manifests when myocardium becomes injured, dies, and is replaced by fibrous scar tissue. Until recently, it was thought that the heart had no ability to regenerate injured cardiomyocytes, but in 2001, Orlic et al. (1,2) fundamentally altered our thinking by showing that mobilized or directly applied bone marrow (BM)–derived progenitor cells improved myocardial function after infarction. With this observation, the race was on to find the methods and cells that would provide the greatest benefit for cardiac regeneration (3).

Cell sources tested for efficacy in cardiac cell replacement include embryonic stem cells, skeletal muscle myoblasts, cardiac-derived progenitor cells, and BM-derived progenitor cells. Studies by Asahara, his colleagues, and others have shown that BM-derived cells positive for the cluster of differentiation 34 (CD34) surface antigen were promising mediators of improvement in cardiac function after injury (4,5). Although these cells do not seem to transdifferentiate in any significant numbers into myocytes (6,7), they do seem to contribute to neovascularization and have paracrine effects that improve cardiac function in animal models (8–11). There is additional evidence showing that these cells may also be helpful in humans (12).

One way to enhance regeneration but avoid the complications associated with allogenic cell application or harvesting and reapplication of progenitor cells is to mobilize them from the BM using colony stimulating factors. In this issue of the *Journal*, Zohlnhöfer et al. (13) perform a meta-analysis of recent trials to assess whether mobilization of $CD34^+$ cells is a viable strategy for cardiac regeneration.

The syllogism

What Zohlnhöfer et al. (13) found was a paradox. If granulocyte colony-stimulating factor (G-CSF) shows a dose-dependent and duration-dependent correlation with $CD34^+$ cell mobilization and if $CD34^+$ cells improve cardiac function, then how can G-CSF have no effect on measures of cardiac function after infarction?

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

Reprint requests and correspondence: Dr. Samuel C. Dudley, Jr, Section of Cardiology, University of Illinois at Chicago/Jesse Brown VA Medical Center, 640 South Wood Street, MC715, Chicago, Illinois 60612. scdudley@uic.edu.

Perfecting the syllogism

Putting aside the criticisms common to any meta-analysis, there are multiple other explanations for this apparent contradiction. The simplest resolution is that mobilized $CD34^+$ cells do not participate in cardiac regeneration. Before $CD34^+$ cell mobilization is dismissed altogether, there are more subtle possibilities that warrant consideration. Foremost is that the combined number of patients treated is insufficient to detect a positive effect. Unfortunately, this possibility would have disturbing implications for the magnitude of any improvement with progenitor cell mobilization and for the number of patients that would need to be treated to have an aggregate benefit.

Another set of explanations revolves around using CD34 to identify a functional and effective progenitor cell for cardiac repair. It is possible that G-CSF failed to mobilize the most effective of cell populations in the bone marrow or that G-CSF stimulation modified the function of $CD34^+$ cells. Modest improvements with the application of unsorted BM-derived cells using multiple sources and handling techniques suggests that there are progenitor cells in the BM with salutary properties, although $CD34^+$ cells only represent approximately 1% of all cells in the BM (14). This suggests that $CD34^+$ cells may not be the only effective cells in the BM. Additionally, there is evidence that G-CSF mobilization, age, renal failure, diabetes, and other athero-sclerotic risk factors adversely affect $CD34^+$ progenitor cell function and thus may not be the best single option for patients with certain cardiomyopathies (15–19). Alternatively, the mobilized $CD34^+$ cells may never have homed to the heart. Testing this supposition points out the need for better tools to assess homing and differentiation in vivo, which are currently limited (20,21). It is also possible that the number of cells mobilized does not reach the dose necessary for cell replacement therapy to work. Currently, groups are directly applying tens of millions of cells to the heart. Although present for longer periods and at elevated levels, mobilization of progenitor cells using G-CSF may not allow for engraftment levels where effects are comparable to those seen with direct application, and cell boluses may be better than more sustained but lower levels over time. It could be that G-CSF and $CD34^+$ cells have equal and opposing effects, but the lack of identified G-CSF–associated complications argues against this. Nevertheless, other mobilizing agents should be considered (22).

Perhaps we are not following the right measures of cardiac function. Despite its predictive value, ejection fraction is a function of load and may not fully reflect effects of cell replacement. On the other hand, Zohlnhöfer et al. (13) point out that infarct size, when available, was also unchanged with therapy.

The good news is that G-CSF used immediately after myocardial infarction seems safe, even with concurrent angioplasty, but this meta-analysis does call into question the idea of administering G-CSF alone after myocardial injury (23). In any event, this article should point the way for definitive trials to resolve an imperfect syllogism.

Acknowledgments

Dr. Dudley has received grants from Pfizer and CV Therapeutics, owns stock in Medtronic and Johnson & Johnson, and has received consulting fees from Ortho Clinical Diagnostics.

References

1. Orlic D, Kajstura J, Chimenti S, et al. Bone marrow cells regenerate infarcted myocardium. Nature. 2001; 410:701–5. [PubMed: 11287958]

2. Orlic D, Kajstura J, Chimenti S, 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. [PubMed: 11504914]
3. Dimmeler S, Zeiher AM. Wanted! The best cell for cardiac regeneration. J Am Coll Cardiol. 2004; 44:464–6. [PubMed: 15261949]
4. Kawamoto A, Tkebuchava T, Yamaguchi J, et al. Intramyocardial transplantation of autologous endothelial progenitor cells for therapeutic neovascularization of myocardial ischemia. Circulation. 2003; 107:461–8. [PubMed: 12551872]
5. Ott I, Keller U, Knoedler M, et al. Endothelial-like cells expanded from CD34+ blood cells improve left ventricular function after experimental myocardial infarction. FASEB J. 2005; 19:992–4. [PubMed: 15814609]
6. Jaquet K, Krause KT, Denschel J, et al. Reduction of myocardial scar size after implantation of mesenchymal stem cells in rats: what is the mechanism? Stem Cells Dev. 2005; 14:299–309. [PubMed: 15969625]
7. Murry CE, Soonpaa MH, Reinecke H, et al. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature. 2004; 428:664–8. [PubMed: 15034593]
8. Simpson D, Liu H, Fan TH, Nerem R, Dudley SC Jr. A tissue engineering approach to progenitor cell delivery results in significant cell engraftment and improved myocardial remodeling. Stem Cells. 2007; 25:2350–7. [PubMed: 17525236]
9. Gnecchi M, He H, Liang OD, et al. Paracrine action accounts for marked protection of ischemic heart by Akt-modified mesenchymal stem cells. Nat Med. 2005; 11:367–8. [PubMed: 15812508]
10. Kinnaird T, Stabile E, Burnett MS, et al. Local delivery of marrow-derived stromal cells augments collateral perfusion through paracrine mechanisms. Circulation. 2004; 109:1543–9. [PubMed: 15023891]
11. Tang YL, Zhao Q, Qin X, et al. Paracrine action enhances the effects of autologous mesenchymal stem cell transplantation on vascular regeneration in rat model of myocardial infarction. Ann Thorac Surg. 2005; 80:229–36. [PubMed: 15975372]
12. Patel AN, Geffner L, Vina RF, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. J Thorac Cardiovasc Surg. 2005; 130:1631–8. [PubMed: 16308009]
13. Zohlnhöfer D, Dibra A, Koppara T, et al. Stem cell mobilization by granulocyte colony-stimulating factor for myocardial recovery after acute myocardial infarction: a meta-analysis. J Am Coll Cardiol. 2008; 51:1429–37. [PubMed: 18402895]
14. Dawn B, Bolli R. Bone marrow for cardiac repair: the importance of characterizing the phenotype and function of injected cells. Eur Heart J. 2007; 28:651–2. [PubMed: 17339263]
15. Choi JH, Kim KL, Huh W, et al. Decreased number and impaired angiogenic function of endothelial progenitor cells in patients with chronic renal failure. Arterioscler Thromb Vasc Biol. 2004; 24:1246–52. [PubMed: 15155385]
16. Edelberg JM, Tang L, Hattori K, Lyden D, Rafii S. Young adult bone marrow-derived endothelial precursor cells restore aging-impaired cardiac angiogenic function. Circ Res. 2002; 90:E89–E93. [PubMed: 12039806]
17. Tepper OM, Galiano RD, Capla JM, et al. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. Circulation. 2002; 106:2781–6. [PubMed: 12451003]
18. Urbich C, Dimmeler S. Risk factors for coronary artery disease, circulating endothelial progenitor cells, and the role of HMG-CoA reductase inhibitors. Kidney Int. 2005; 67:1672–6. [PubMed: 15840010]
19. Honold J, Lehmann R, Heeschen C, et al. Effects of granulocyte colony stimulating factor on functional activities of endothelial progenitor cells in patients with chronic ischemic heart disease. Arterioscler Thromb Vasc Biol. 2006; 26:2238–43. [PubMed: 16902165]
20. Brenner W, Aicher A, Eckey T, et al. ^{111}In-labeled CD34+ hematopoietic progenitor cells in a rat myocardial infarction model. J Nucl Med. 2004; 45:512–8. [PubMed: 15001696]
21. Kraitchman DL, Tatsumi M, Gilson WD, et al. Dynamic imaging of allogeneic mesenchymal stem cells trafficking to myocardial infarction. Circulation. 2005; 112:1451–61. [PubMed: 16129797]

22. Aicher A, Zeiher AM, Dimmeler S. Mobilizing endothelial progenitor cells. Hypertension. 2005; 45:321–5. [PubMed: 15655116]

23. Ince H, Nienaber CA. Future investigations in stem cell activation with granulocyte-colony-stimulating factor after myocardial infarction. Nat Clin Pract Cardiovasc Med. 2007; 4 (Suppl 1):S119–22. [PubMed: 17230209]