EDITORIAL COMMENT

An Imperfect Syllogism
Granulocyte Colony-Stimulating Factor Mobilization and Cardiac Regeneration*

Samuel C. Dudley, Jr, MD, PhD, FACC,†‡
David Simpson, BS†
Chicago, Illinois

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?

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 atherosclerotic 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 frac-

*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.

From the †Division of Cardiology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois; and the ‡Jesse Brown VA Medical Center, Chicago, Illinois. 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.
 tion 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.

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. E-mail: scdudley@uic.edu.

REFERENCES