The End of Granulocyte Colony-Stimulating Factor in Acute Myocardial Infarction?

Reaping the Benefits Beyond Cytokine Mobilization

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“The wing of a bird may be, it will never enable the bird to fly if unsupported by the air. Facts are the air of science. Without them a man of science can never rise.”

—Ivan Pavlov

Facts must be sought from the rigorous application of scientific method. Indeed, the hardest questions sometimes require the hardest methods. Having a tool that can answer the questions with the minimum number of side effects in the minimum number of patients must be the desire of all clinical investigators who wish to generate new facts and contribute to the pool of knowledge. Progress in cell therapy for cardiovascular disease has been hindered at both the preclinical and clinical stages, perhaps because the appropriate tools to address the pertinent questions have not been used. In this context, magnetic resonance imaging (MRI) has, by necessity, rapidly evolved as the ideal tool for surrogate end-point measurements in early-phase clinical trials. In this issue of Circulation, Ripa and colleagues have elegantly demonstrated the utility and maturation of this technology in their study of granulocyte colony-stimulating factor (G-CSF) as an adjunctive therapy to mechanical reperfusion after myocardial infarction.

Cardiovascular cell transplantation and cytokine mobilization originated in clinical trials with the explicit goal of myocardial regeneration, but more recently, the emphasis has been focused on “remodeling attenuation” therapy, in which the presumed mechanism has shifted from the “replacement” capacity of transplanted cells to their “paracrine” effects. This thesis becomes more convincing given the lack of cardiomyogenic transdifferentiation demonstrated by adult hematopoietic stem cells. Despite the indistinct mechanism, the early-phase, nonrandomized clinical studies of G-CSF showed similar degrees of change, with no significant differences seen between the treatment and control arms. Despite these findings, this study does have some limitations, but these are mostly related to the concept of using G-CSF as sole therapy rather than as an adjunct therapy for cell mobilization and subsequent harvesting. In addition, MRI, although the gold standard, is not the perfect imaging modality given that there are some difficulties in scanning every patient because of the presence of implantable pacemaker and defibrillator devices, as well as claustrophobia.

Interestingly, these data also correlate with another recent study that used G-CSF after myocardial infarction. In that study, G-CSF was used at the same dosing level but for 1 less day (10 μg/kg for 5 instead of 6 days), also to no effect. The primary end point in that study was reduction of LV size measured by 99mTc sestamibi scintigraphy. The secondary end point of LV ejection fraction assessment actually demonstrated a slightly greater (but nonsignificant) increase in the placebo group compared with the treatment group. Further-more, in previous studies using G-CSF in chronic myocardial ischemia, there actually appeared to be a deterioration in regional measures of LV function and perfusion in patients treated with G-CSF. The accumulated data from the 2 randomized, placebo-controlled studies of G-CSF in myocardial infarction are difficult to reconcile with a similar study reported by Ince et al. It could be speculated that this is
attributable to differences in the study design, such as timing of G-CSF injection, and that the method of LV function assessment, namely, transthoracic echocardiography including use of dobutamine stress, is not equivalent to cardiac MRI in terms of either sensitivity or specificity.14

What are the lessons for cardiac cell transfer after acute myocardial infarction, and how may patients reap the benefits beyond cytokine mobilization? Will G-CSF simply join the vast selection of other experimental agents designed to aid myocardial infarction healing that did not live up to their preclinical and early-phase clinical hype? Perhaps it will find its true role as a means to harvest peripheral blood mononuclear cells for the purposes of ex vivo manipulation and direct delivery. At least when administered in the context of recent acute myocardial infarction, this approach would appear to be safe,1,10,13 although doubts were raised previously about its safety in both acute and chronic myocardial ischemia.11,12,15 Future cell mobilization research should be directed to alternative agents that can lead to targeted release of stem and progenitor cell populations, without the release of potentially proinflammatory cells such as neutrophils.16

In contrast to the concept of cytokine-mediated mobilization, the promise of autologous cell transfer to augment LV recovery has recently been supported by the results of the double-blind, randomized, placebo-controlled REPAIR-AMI trial (Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction).17 That study showed a significantly higher improvement in LV ejection fraction compared with placebo injection. Although the overall effect was moderate and MRI was not used for the natural history of regional myocardial recovery demonstrated by these 2 recently reported G-CSF studies,1,10 No study has convincingly demonstrated any sustained benefit beyond the 4- to 6-month period, and in this regard, the randomized but not placebo-controlled BOOST trial (BOne marOw transfer to enhance ST-elevation infarct regeneration) suggested only acceleration of LV recovery without long-term benefit on LV function after coronary cell transfer.18 If these data are later corroborated by long-term follow-up of REPAIR-AMI patients, several new hypotheses need to be addressed in future clinical research. Among these, the hypotheses of dose dependency, purification of a homogeneous mononuclear cell fraction, enrichment for particular cell types such as CD34+ or CD133+ cells,19 and pharmacological modifications to enhance engraftment and functional effect are warranted. When these trials are designed, however, lessons from the studies on cytokine mobilization should be taken into account. First, the choice of a primary end point and imaging modality should be chosen with relevance to the potential clinical impact. Most trials use conventional change in global LV ejection fraction as a primary end point, but the effect of cell transfer on this end point may be clouded by later effects of β-blockade or angiotensin-converting enzyme inhibitors on infarcted or remote segments. Instead, end points that reflect morphological changes such as infarct size20 or functional analysis of regional wall motion in the infarct area may be more appropriate. Cardiac MRI is the current state-of-the-art technique to address these issues in a repetitive manner with high spatial resolution that outmatches the power of conventional LV angiography or other noninvasive techniques by providing the needed information in 1 session.8,9

Optimal timing in relation to reperfusion and infarct healing also appears to be a common issue in G-CSF1,10,13 and coronary cell transfer trials.17,18,20 For instance, conflicting results of the REPAIR-AMI trial and the study by Janssens et al13 on LV recovery may relate to differences in timing of cell transfer. Thus, future cell therapy studies should apply cell transfer in a manner that is consistent with the time course of myocardial healing and homing signals. Conceptual risks for atherosclerosis should be addressed with direct imaging of the vascular wall in combination with observation of the physiological impact on epicardial segments downstream from cell transfer.22,23 Imaging modalities such as intravascular ultrasound or virtual histology24 should give more precise answers to this than quantitative coronary angiography.

The present study by Ripa et al13 answers previous critics of published cell therapy studies who have pointed out that the margin of change seen in the control groups did not match their experience in clinical practice. However, in so doing, this study also sets the bar considerably higher for future studies. To proceed with further clinical studies without the use of cardiac MRI will expose too many patients to potential side effects of these new biological therapies. As clinical investigators, we have a duty to use the best available means of measurement to generate the knowledge that will progress the field of cardiovascular cell therapy.

Disclosures

None.

References


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