G-CSF administration in acute myocardial infarction: what is the best timing? Reply

We welcome the interest of Maggiolini and colleagues in our recent article on granulocyte colony-simulating factor (G-CSF) in acute myocardial infarction (AMI),1 arguing for early (hours rather than days) G-CSF administration in relation to its observed beneficial effects in functional recovery post-AMI. Indeed, mixed outcomes from clinical trials point to several outstanding issues that await further investigation. Chief among them is a clinically practicable window of G-CSF administration for cytokine-mobilized stem cell therapy. We agree with the authors that meta-analysis has indicated a positive correlation between G-CSF timing and left ventricular ejection fraction (LVEF) outcome, though current available literature on this topic remains controversial and consensus has yet to emerge. The crux of the issue stems from the following issues:

(i) The challenging task of comparing results from different patient cohorts of published trials. A number of other key variables such as the time to reperfusion by percutaneous coronary intervention (PCI), the initial clinical status of enrolled patients (e.g. large or small infarct size, LV dysfunction, depressed ejection fraction), and selective use of mobilized cell types (e.g. CD34 purified or CD133 selected populations) in reinfusion studies1 are likely to play crucial roles in the observed outcomes. Subgroup analysis of patients in REPAIR-AMI2 (mean baseline LVEF <48.9%), results from Perin et al.3 (mean baseline LVEF 20%) and TOPCARE-AMI4 (baseline LVEF as a predictor of favourable remodelling) trials showed that greater recovery of functional status was achieved in patients with depressed LV function. As highlighted by Achilli et al.,5 compared with other similar trials, the baseline LVEF of their enrolled patients was significantly depressed (mean LVEF <45%). This, together with relatively early (<12 h) time to reperfusion (although similar to REVIVAL-25 and STEMIMI7 trials that found no significant change in LV function after G-CSF therapy) and high CD34+ cell mobilization, could have favourably impacted outcome secondary to the time of G-CSF administration post-PCI.

(ii) Different imaging modalities were utilized in assessing functional improvements across different trials. As reported in their study, Achilli et al.6 did not find significant LVEF improvement by MRI and echocardiography during a 6 month follow-up comparing G-CSF vs. placebo groups. However, infarct size reduction demonstrated by a reduced number of transmural late gadolinium enhancement segments was noted in the G-CSF group. This suggests that G-CSF therapy improved regional but not global function despite early administration (9.2 ± 2.7 h post-PCI). Direct influence of G-CSF on myocardial tissues may be a contributing factor in the recovery. G-CSF has been reported to inhibit apoptosis in cardiomyocytes,8 to promote myocardial angiogenesis,9 and to induce activation of resident cardiac stem cells (CSC)10 in experimental models. Moreover, G-CSF receptor levels in the myocardium are low, but increase gradually by Day 4–5 post-PCI.11 Critical subgroup analysis of poor mobilizers of circulating stem cells following G-CSF administration may expound this unique direct autocrine/paracrine effect on resident myocytes and CSCs in exacting functional improvements.

(iii) Cumulative positive experiences from Suarez de Lezo et al.12 and RIGENERA13 that deployed a late (>5 days post-PCI) strategy may lend support to a delayed therapeutic G-CSF window, though a similar strategy did not yield positive results from REVIVAL-2.6 Temporal mismatch between activation of SDF-1 (a stem cell homing factor) and circulating stem cells early post-PCI,14 together with a hostile myocardial environment, may discourage homing and engraftment of the mobilized circulating stem cells during the acute phase.1 Similarly, early intracoronary introduction (<24 h post-PCI) of bone marrow-harvested stem cells did not yield significant benefits on LV function at a 4 month follow-up.15

Current available evidence shows that the ideal time for G-CSF administration in cytokine-mobilized stem cell therapy post-AMI is far from clear. Although Engellmann et al.14 and Overgaard et al.15 had previously demonstrated insensitivity of LV functional recovery to G-CSF timing, carefully designed and well-controlled randomized trials that are adequately sample sized for subgroup analysis in this respect would be highly anticipated.

References


Winston Shim*  
Research and Development Unit, National Heart Centre (SingHealth), Singapore

Ashish Mehta  
Research and Development Unit, National Heart Centre (SingHealth), Singapore

Chong Hee Lim  
Department of Cardiothoracic Surgery, National Heart Centre (SingHealth), Singapore

Terrance Chua  
Department of Cardiology, National Heart Centre (SingHealth), Singapore

Philip Wong  
Department of Cardiology, National Heart Centre (SingHealth), Singapore

*Corresponding author: National Heart Centre Singapore, 17, Third Hospital Avenue, Mistri Wing 168752, Singapore. Tel: +65 64 350 752; fax: +65 62 263 972, Email: winston.shim.s.n@nhcs.com.sg