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

We read with great interest the comprehensive review by Shim et al., which critically examines possible reasons related to the mixed results of granulocyte colony-simulating factor (G-CSF) to recover ventricular function after an acute myocardial infarction (AMI). The authors correctly underlined that timing for administration is one of the crucial factors in deciding the outcome of G-CSF. They have suggested that the maximal benefit is likely to be achieved when G-CSF is administered 5 days after the acute event. To support this statement, the authors quoted among others Engelmann et al. and Wang et al. However, the first of these papers stated that neither early nor late G-CSF administration was able to improve left ventricular (LV) function, and myocardial perfusion was improved by early therapy only. Further, the second paper reported that in patients with a very large myocardial infarction there is a peak in the levels of circulating mesenchymal cells the third day after the acute event.

We feel that a critical review of our experience in the STEM-AMI trial and of available experimental and clinical data seem to support an opposite conclusion: G-CSF administration as early as possible after AMI is likely to generate more pronounced perfusional and functional benefits. This inference may be sustained from different standpoints:

(1) From a biological point of view, it has been shown that the natural course of healing the infarction and the presence of homing signals within the damaged myocardium appear to favour cell engraftment in the early days after reperfusion. However, the adverse inflammatory environment might be deleterious if cells nest too early after reperfusion. A favourable milieu between inflammation and cell engraftment appears to be reached after the fifth to seventh day after AMI. An ‘early’ G-CSF administration strategy promotes a peak of circulating progenitors 5–6 days after reperfusion, thus taking advantage of such a putative ‘therapeutic window’. This hypothesis is corroborated by the finding that the major benefit in improvement of ejection fraction (EF) was noted when an intracoronary bone marrow-derived cell infusion was administered 4 days after AMI.7

(2) Experimental evidence in rodent models of coronary ligation has suggested that the beneficial effects of G-CSF were observed when therapy was started before or shortly after ischaemic injury, and early initiation of G-CSF therapy resulted in better outcomes.8 More interestingly, a large animal study assessing early and delayed administration of G-CSF in a porcine model of myocardial infarction and reperfusion has shown that early treatment with G-CSF after AMI decreases ventricular dilatation, whereas delayed treatment has a deleterious effect on LV remodelling.9

(3) Clinical evidence is not yet conclusive in supporting an exact timing of G-CSF administration after AMI in humans. However, a meta-analysis by Abdel-Latif et al. of randomized controlled trials of G-CSF therapy in patients with AMI has suggested by subgroup analysis that the only two factors possibly related to an EF benefit were ventricular dysfunction at baseline and early G-CSF administration. In addition, it has to be mentioned that in several AMI trials showing myocardial functional improvement, G-CSF treatment was started within 24–48 h from primary angioplasty (Valimigil, FIRST-LINE, Kueht, Takano). Moreover, the clinical trials cited by Shim et al. using G-CSF mobilized and re-infused bone marrow stem cells showed that G-CSF was effective in improving LVEF only when started within 48 h from PTCA (MAGIC II, MAGIC cell-3-DES, Steinwender). Finally, in our recent STEM-AMI trial, a significant reduction of unfavourable remodelling was observed at 6 months in patients with anterior AMI and severe ventricular dysfunction after successful percutaneous intervention who received an early administration (<12 h from symptoms onset) of high-dose G-CSF.

On the basis of the aforementioned data, we feel that the ‘early’ G-CSF regimen should be taken into a consideration when designing future clinical trials with AMI patients.

References
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