Revival of cytokine therapy in heart failure?

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This editorial refers to ‘Randomized trial of combination cytokine and adult autologous bone marrow progenitor cell administration in patients with non-ischaemic dilated cardiomyopathy: the REGENERATE-DCM clinical trial’1, by S. Hamshere et al., on page 3061.

Dilated cardiomyopathy (DCM) and heart failure is a serious disease with a high morbidity and mortality rate in spite of optimal medical therapy. Although coronary artery disease is the main aetiology for the condition, a large group of patients have non-ischaemic DCM.

Regenerative therapy with stem cells has been a focus to improve cardiac function, physical performance, and quality of life, and to reduce morbidity and mortality in these severely diseased patients. The focus was initially on cell sources from the bone marrow, but recent studies have extended interest to cells from many different tissues such as adipose tissue, heart, umbilical cord, etc., (Figure 1).

Cytokine therapy with granulocyte colony-stimulating factor (G-CSF) has for many years been used in haematology to mobilize stem cells from the bone marrow into the blood for transplantation. The use of G-CSF for regenerative stem cell therapy in cardiac disease was intensively studied pre-clinically and clinically a decade ago (Figure 2).

Several studies were conducted with subcutaneous injections of G-CSF for 5–7 days in patients with acute ST-segment elevation myocardial infarction (STEMI), heart failure, or refractory angina.3–6 The theory was that the mobilized stem cells from the bone marrow would pass via the blood through the cardiac circulation and be attracted to cardiac tissue areas with acute or chronic ischaemia or reduced myocyte function. The stem cells could then either differentiate into cardiac/endothelial cell or stimulate cardiac tissue to regenerate diseased tissue and improve cardiac pump function and perfusion. However, several well performed and controlled studies could not demonstrate any effect of G-CSF therapy alone on cardiac regeneration.3–4

This rather disappointing result led to new theories for the use of G-CSF. The focus now shifted to some of the cell populations mobilized from the bone marrow. The CD34+ and CD133+ mononuclear cells (MNCs) in particular were considered of importance for regenerative therapy. Therefore, studies were conducted with collection of these cell populations without or after subcutaneous G-CSF therapy. The isolated subpopulations were then injected via either the intracoronary or the transendocardial route into the myocardium in patients with STEMI, heart failure, or refractory angina.5–10 However, intracoronary infusion of MNCs or the CD34+ CXCR4+ subpopulation of cells isolated from bone marrow was without any effect in acute myocardial infarction.5 To increase the number of CD34+ cells for therapy, the cells were then isolated from the peripheral blood by apheresis after subcutaneous injections of G-CSF. A phase II study in patients with refractory angina with direct transendocardial myocardial injection of mobilized CD34+ demonstrated improvement in exercise capacity and symptoms.5 However, the confirmatory phase III trial was initiated but later stopped before completion probably due to the low rate of recruitment.7

In this issue of the journal, Dr Hamshere and colleagues present results from the REGENERATE-DCM trial in 60 patients with non-ischaemic DCM.8 They introduce a new concept with a combination of subcutaneous G-CSF therapy for 5 days with mobilization of stem cells from the bone marrow followed by intracoronary infusion of bone marrow aspirated MNCs.

In a rather complex randomized placebo-controlled trial design, the patients were divided into four groups: the ‘peripheral placebo group’ who received peripheral subcutaneous injected saline, the ‘peripheral G-CSF group’ who received subcutaneous G-CSF alone, the ‘intracoronary (IC) BMC group’ who underwent bone marrow harvest after G-CSF and received intracoronary infusion of autologous MNCs, and the ‘IC serum group’ who underwent bone marrow harvest after G-CSF but received intracoronary infusion of serum only.

At 3 months follow-up, peripheral G-CSF combined with intracoronary MNC therapy was associated with a 5.37 percentage point increase in left ventricular ejection fraction (LVEF) (to 38.30 ± 12.97% from 32.93 ± 16.46%, P = 0.0138), which was maintained for 1 year. There was also a decrease in New York Heart Association (NYHA) classification and N-terminal pro-brain natriuretic peptide (NT-proBNP), and improved exercise capacity and quality of life. No significant change in LVEF was seen in the remaining treatment groups.

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These results are in agreement with three small non-controlled studies with intracoronary or transendocardial treatment with G-CSF-mobilized CD34+ cells in patients with non-ischaemic DCM. In the patients, transendocardial CD34+ cell transplantation was associated with higher myocardial retention rates and greater improvement in ventricular function, NT-proBNP, and exercise capacity compared with the intracoronary route. Moreover, it has been demonstrated that the remaining myocardial perfusion scores improved, in addition to the LVEF and 6-min walking distance, for up to 5 years after intracoronary infusion of CD34+ cells.

Hamshere and colleagues also demonstrate a very high number of circulating CD34+ cells (from 3.94 to 56.79/μL, average) mobilized from the bone marrow after G-CSF stimulation. An average of 216 × 10^6 MNCs was injected by the intracoronary route and 2.26% (4.9 × 10^6) were CD34+ cells.

The results in the REGENERATE-DCM trial are rather convincing in spite of the relatively small patient population in the four groups. However, the design of the study raises several questions, some of which are also addressed by the authors.

It can be debated as to whether G-CSF stimulation is needed for improvement of myocardial function in non-ischaemic DCM or whether MNCs alone could have an identical effect. Potentially, and unanswered by the study design, MNC therapy alone could be equally effective.

What is left in the bone marrow after G-CSF mobilization of stem cells? Is there a depletion of CD34+ cells and other cell subpopulations from the bone marrow, which reduces the number of potential beneficial active cells for bone marrow aspiration and harvesting? This does not seem to be the case when considering the results. However, will there then be relatively more of other non-mobilized cell populations such as the mesenchymal stromal cells in the aspirate, which recently have demonstrated improvement in left ventricular end-systolic volume and LVEF in a double-blind placebo-controlled design in patients with ischaemic heart failure?

The results are an important contribution to the ongoing discussion of whether MNCs from bone marrow aspirates should or should not be considered a new regenerative therapy in heart disease since the results are conflicting. A recent meta-analysis pooling published studies have described an effect of MNC therapy on the risk of mortality and re-hospitalization caused by heart failure, and an advantage of stem cell treatment for performance status and exercise capacity, LVEF, and quality of life. In another meta-analysis, transplantation of MNCs improved LVEF, reduced infarct size, and ameliorated remodelling in patients with ischaemic heart disease.

These findings are in conflict with another recent analysis using the individual patient data from several of the studies also involved in the meta-analyses. In patients with a recent acute myocardial infarction (AMI), no effect of cell therapy was demonstrated on major adverse cardiac and cerebrovascular events, death, or death/AMI recurrence/stroke in comparison with controls. The same was found for changes in LVEF, end-diastolic volume, and end-systolic volume.

In summary, the study by Hamshere et al. is a very important and promising contribution to the present knowledge within regenerative cell therapy in patients with non-ischaemic DCM and potentially beneficial active cells for bone marrow aspiration and harvesting.
also in ischaemic DCM patients. The results demonstrate a beneficial effect of G-CSF treatment combined with intracoronary infusion of bone marrow aspirated MNCs. Although many questions are still unanswered, the study indicates that G-CSF therapy potentially should still be considered in heart disease combined with MNCs or other promising cell lines.

Conflict of interest: none declared.

References
Lipoma of the interventricular septum

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A 49-year-old man without cardiovascular risk factors and a negative cardiovascular history was referred to our Hospital for further characterization of a solid, hyperechoic mass in the mid portion of the interventricular septum (Panel A), incidentally found on a check-up transthoracic echocardiogram. The cardiac magnetic resonance (CMR) study showed a well-defined ovoid mass, diameter 29 × 17 mm, located in the mid portion of the interventricular septum. The mass’ signal was hyperintense on T1-weighted sequences (Panel B), with a complete signal suppression after a fat-saturation prepulse (Panel C). In fat-saturated oedema images (“T2 STIR”), the mass was hypointense, further confirming the solid, hypovascular nature of the content. No signs of fibrosis were evident at late gadolinium enhancement study (Panel D). These findings are diagnostic for an intramyocardial lipoma.

Cardiac lipomas are benign, encapsulated tumours, composed of mature fat cells, usually located in the interatrial septum: they account for 5% of primary cardiac tumours. Lipomas of the interventricular septum are extremely rare, with a prevalence of <1 of 1000 benign cardiac tumours. Their diagnosis is often incidental: the clinical symptoms of cardiac lipomas are non-specific, often absent and mainly related to their location and size. Surgical resection is recommended in symptomatic patients with intractable arrhythmias or flow obstruction within the heart. Treatment strategy is a dilemma when the patient is asymptomatic, and no guideline exists. This patient was managed with an implantable loop recorder in order to monitor over time the presence and frequency of ventricular arrhythmias.

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