It is never too late for native cardiac repair: can genes awake the Sleeping Beauty in chronic patients?

Ricardo Sanz-Ruiz1,2 and Francisco Fernández-Avilés1,2*

1Department of Cardiology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IISGM); and 2Universidad Complutense de Madrid, Madrid, Spain

Online publish-ahead-of-print 12 June 2015

This editorial refers to ‘Changes in ventricular remodelling and clinical status during the year following a single administration of stromal cell-derived factor-1 non-viral gene therapy in chronic ischaemic heart failure patients: the STOP-HF randomized Phase II trial’\(^\text{2}\), by E.S. Chung et al., on page 2228.

Chronic heart failure (CHF), mainly caused by ischemic heart disease (IHD), represents the leading cause of disability and death in developed countries. The current standard of care does not provide a definitive solution for this condition, except for cardiac transplantation, which is hampered by the scarcity of organs and by rejection.\(^\text{1}\)

Thus there is a compelling need for innovation in this field, in which regenerative medicine has emerged as the most promising hope for millions of patients worldwide.

In this issue of the European Heart Journal, Chung and colleagues\(^\text{2}\) report the results of a double-blind phase II clinical trial to assess the safety and efficacy of plasmid stromal cell-derived factor-1 (pSDF-1) in patients with CHF. Ninety-three patients with end-stage IHD were randomized 1:1:1 to receive transendocardial injections of 15 mg or 30 mg of pSDF-1 or placebo. The primary endpoint was a composite of 6-min walk distance and quality of life [Minnesota Living with Heart Failure Questionnaire (MLWHFQ)] at 4 months, which was safely improved in the high-dose group. This clinical benefit was extended to 12-months follow-up and was accompanied by improvements in ventricular remodelling, especially in those patients with the most severe ventricular dysfunction.\(^\text{2}\)

The Screening to Prevent Heart Failure (STOP-HF) trial constitutes an important breakthrough in the field of cardiac repair, demonstrating for the first time the safety and clinical benefits of plasmid DNA administration in CHF patients. Like in the only published phase II gene therapy trial to date,\(^\text{3}\) very sick patients on optimal treatment were included (median ejection fraction 29% due to 10-year-old scars), representing the most challenging population for cardiac repair, since cardiac cells are lost and extracellular matrix is definitely disassembled. Chung and colleagues\(^\text{2}\) demonstrate that the activation of the SDF-1–CXCR4 axis is possible even in these advanced stages of IHD with evident clinical benefits. The SDF-1–CXCR4 axis orchestrates stem cell homing into the myocardium after ST-segment elevation myocardial infarction, but only for a few days after the ischemic event.\(^\text{4}\) It also plays a role in the adverse ventricular remodelling process, having anti-apoptotic effects, inducing angiogenesis, inhibiting fibrosis and improving contractility in the scar border zone (Figure 1).\(^\text{3–6}\)

What is somehow impressive is that gene therapy is able to reactivate native cardiac repair mechanisms in a completely unstructured tissue, promoting the expression of stem cell homing signals otherwise no longer found. This observation by itself justifies further investigations in the form of phase III clinical trials.

The first era of myocardial regeneration, mainly based on stem cell delivery into the injured myocardium, changed the dogma of the non-reparative potential of the heart, brought physicians closer to cardiac biology and allowed us to understand the intricate network of molecular and cellular healing processes that could be therapeutically modified after an ischemic insult to prevent CHF. However, this ‘stem cell–based’ approach has been proved ineffective to repair the heart in advanced phases of IHD. Therefore, along with promising advances in cell-based tissue engineering, new types of ‘non-cellular’ regenerative treatments are being explored.\(^\text{7}\) Among them, the manipulation of the genetic material that governs cardiac cell function is the most realistic.

Gene therapy is defined as the technology by which genes, small DNA or RNA molecules are delivered to a target cell or organ to treat or to prevent diseases.\(^\text{8}\) Sequencing of the human genome and new developments in the field of gene transfer vectors have provided us with the necessary tools to target specific genes that determine cardiac diseases. Since the first clinical trial in 1998,\(^\text{8}\)
more than 200 cardiovascular gene therapy studies have set the principles for an evidence-based modification of gene expression to improve angiogenesis, protect the myocardium or regenerate dead tissue. Successful delivery of genetic material to the myocardium is paramount to achieve therapeutic efficacy, and can be done using viral and non-viral vectors. Non-integrative vectors, like adenoviruses and specifically adeno-associated viruses (AAV), are considered today the most suited viral vectors for myocardial gene delivery, but have the drawbacks of vector size, slow gene expression kinetics, immune deleterious responses and a high prevalence of neutralizing antibodies in the general population. A non-viral vector (i.e., naked single-stranded DNA or ‘plasmid DNA’) was used in the STOP-HF trial based on good safety and efficacy profiles observed in a previous phase I trial and other clinical studies. Plasmid DNA shows low production costs, unlimited transgene size, low toxicity and low immunogenicity. Although the poor transduction efficiency of non-viral vectors requires high doses of plasmid and invasive delivery strategies, the results of the STOP-HF trial suggest that a single dose of pSDF-1 is enough to exert a beneficial effect on left ventricular performance in advanced stages of IHD. Furthermore, and like the authors suggest, it is easy to hypothesize that repeat administration of pSDF-1 may elicit even further improvements. Regarding the need for transendocardial injections, plasmid DNA like the one used by Chung and colleagues can be effectively injected in the myocardium using a variety of percutaneous catheters. The Helical infusion catheter (Biocardia, San Carlos, CA, USA) has shown good safety and efficiency profiles in several cell-based trials, which have been replicated in the STOP-HF trial. Today, at least 22 genes can be targeted in the cardiovascular scenario, 7 of them in CHF patients. Novel exciting targets are constantly being described, like the recent demonstration that telomerase activation with AAV9-Tert restores telomere length and improves survival in a mouse model of myocardial infarction. Furthermore, new biotechnological developments for gene and vector design have improved myocardial tropism, gene expression efficiency, safety and cost-effectiveness and have reduced immunogenicity of viral vectors. Only a faster translation from small to large animals to humans and more expedited evidence-based negotiations with regulatory agencies are needed to move the field forward. If all these breakthroughs are gained in the short term,
gene therapy may move ahead of stem cell therapy and show exciting benefits in phase III clinical trials.

Conflicts of interest: none declared.

References

Editorial