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Skeletal myoblasts for myocardial regeneration in patients with congestive heart failure: where have all the answers gone?

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Over the past decade, excitement has grown regarding the use of stem cells for cardiovascular disease[1]. During that time, considerable progress has been made for patients with acute myocardial infarction and refractory angina[2-4]. Positive, placebo-controlled, phase II trials have been completed and large, well-designed, multicentre trials are underway or will begin soon[5,6]. In addition, a growing number of positive trials have been completed in patients with critical limb ischaemia[7]. While guideline-based therapy is still forthcoming, stem cells likely will provide benefit in patients with these diverse conditions. In contrast, for patients with congestive heart failure (CHF) – for many scientists the ultimate target for cell-based myocardial regeneration – the progress has been excruciatingly slow.

In this issue of EuroIntervention, Duckers et al report the result of the SEISMIC trial, a phase IIa, multicentre, open-label trial comparing patients treated with autologous skeletal myoblasts to a patient control group receiving optimal medical therapy. The trial enrolled 40 patients with ischaemic cardiomyopathy, New York Heart Association (NYHA) Class II and III with left ventricular ejection fraction (LVEF) between 20-45% and a documented akinetic segment, at 13 European sites from October 2005 to May 2007. Patients were required to be on optimal pharmacologic therapy for at least two months prior to screening and have an ICD implanted at least six months prior to randomisation. Treatment was a range of 150 to 800 million (mean 596±194×106) autologous, cultured skeletal myoblasts delivered directly into the ventricular scar. In addition to the ICD requirement, patients received prophylactic amiodarone (200 mg) for four weeks prior to and following cell delivery. The primary safety endpoint, the proportion of patients experiencing serious adverse events at three and six months was similar between the cell treatment and medical control group. Likewise, there was no difference in the primary efficacy endpoint, global LVEF at six months assessed by a MUGA scan, which decreased from 32.3±9.1% to 31.5±11% in myoblast-treated patients compared with a change from 32.6±11.1% to 32.5±8% in the medical control group. Despite the disappointing LVEF results, there were suggestions of improvement in NYHA classification, the Minnesota Living with Heart Failure Questionnaire and the six-minute walk test. The results of the SEISMIC trial raise several issues regarding the current state of cardiovascular cell therapy for patients with CHF.

Cell therapy for congestive heart failure

As the population ages and cardiovascular mortality declines, there is a large and growing population of patients with CHF, a heterogeneous disease resulting from both ischaemic (60%) and non-ischaemic (40%) aetiologies. Remarkable progress has been made in both medical and device therapy for patients with CHF over the last 20 years. In general, pharmacologic therapies with beta blockers and ACE inhibitors or device therapy with biventricular pacing or ICDs are successful, regardless of the aetiology of CHF. In contrast, successful stem cell therapy for CHF may well require an

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aetiology-specific approach. For example, the NIH-sponsored FOCUS trial targets CHF patients with Canadian class II-IV angina or NYHA class II-III heart failure and LVEF ≤45%. Patients are required to have areas of myocardium not amenable to revascularisation with reversible myocardial ischaemia. The targeted myocardial ischaemic area must show electrical viability by NOGA electromechanical mapping based on unipolar voltage of >6.9 mv. Eligible patients receive intramyocardial injection of 100 million autologous bone marrow mononuclear cells into the ischaemic zone[9]. In contrast, similar to the SEISMIC trial, the MARVEL trial enrolled NYHA class II-IV CHF patients with LVEF <35% who received cultured autologous skeletal myoblasts injected into the area of scar based on unipolar voltage <7.0 mv by NOGA[10]. The FOCUS trial is seeking to stimulate angiogenesis, to increase myocardial perfusion and subsequently improve LV function. In contrast, patients enrolled in MARVEL had normal blood flow, and the goal was to stimulate myogenesis in an attempt to improve LV function. Therefore, despite similar symptoms, LV function and required baseline therapy, CHF patients enrolled in FOCUS would be excluded from MARVEL, and vice versa. This is an important paradigm shift in the design of CHF clinical trials. Myocardial regeneration is a complex process and likely requires more than simple angiogenesis or myogenesis to rebuild living, viable muscle. Understanding the process and the solution in the CHF patient with previous MI and scar remains the major challenge in cardiovascular stem cell therapy. This was the problem addressed in SEISMIC and the cell of choice was autologous skeletal myoblasts.

Skeletal myoblasts for CHF

As the authors note, the choice was based on a rational hypothesis, strong preclinical data and promising phase I clinical trials. Skeletal myoblasts, which are resistant to ischaemia and oxidative stress, can be derived autologously and cultured successfully[11]. In preclinical models, skeletal myoblasts were shown to engraft successfully, develop characteristics of cardiac myocytes and contribute to a dose-dependent improvement in left ventricular function[11-13]. The initial clinical studies using skeletal myoblasts which began in 2000 were followed by a series of phase I trials using skeletal myoblasts alone or in conjunction with CABG[15-20]. Successful cell survival and differentiation into mature myofibers was documented in three of four explanted hearts of end-stage CHF patients who had received 300 million skeletal myoblasts in conjunction with left ventricular assist device awaiting cardiac transplantation[21]. In the only published randomised trial, 97 patients received 400 or 800 million myoblasts compared with placebo into a myocardial scar in conjunction with CABG. While there was no improvement in LVEF compared to placebo, myoblast-treated patients had a decrease in LV volume[22]. Importantly, contrary to SEISMIC, patients enrolled in the MAGIC trial were candidates for revascularisation.

Are skeletal myoblasts safe and/or effective?

A critical issue with the use of skeletal myoblasts is the increase in ventricular arrhythmias reported shortly after transplantation in several trials[11,14,17]. Based on the SEISMIC trial results, it appears that periprocedural amiodarone, in conjunction with a previously placed ICD, may be effective in preventing this life-threatening complication. Is there clearly an association with ventricular arrhythmias and is it detrimental? Likely, the truth is somewhere in the middle, where an increase in arrhythmias may occur as electrically active cells integrate and differentiate in scarred myocardium, but if managed, may lead to benefits of myogenesis[11]. The definitive answer was expected to come from the MARVEL trial designed to be a 330 patient, randomised, placebo-controlled phase IIb-III trial to determine the safety and efficacy of percutaneously delivered autologous skeletal myoblasts. Patients were to receive placebo, 400 or 800 million skeletal myoblasts into a defined area of previous myocardial infarction. Unfortunately, the trial stopped early due to limited financial resources with only 20 patients treated. Similar to the phase I dose escalation MYOHEART trial and SEISMIC, there were suggestions of improvement in both the six-minute walk test and the Minnesota Living with Heart Failure score with no significant improvement in LVEF. In contrast to SEISMIC, there was a significant increase in ventricular arrhythmias related to the delivery of skeletal myoblasts. However, recognition and adoption of periprocedure amiodarone appeared to be successful as in SEISMIC. Unfortunately, we may never know the definitive answer to either safety or efficacy of myocardial regeneration with skeletal myoblasts given the financial challenges of an adequately powered phase III trial.

Conclusion

Rebuilding and sustaining muscle in a terminally scarred myocardium is not a simple process and remains a major unmet clinical need. Expecting that one cell type is able to accomplish this task may be unrealistic. More than a decade of clinical work with skeletal myoblasts culminating in a single 40-patient clinical trial illustrates the tremendous challenge that still lies ahead of us.

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