Stem Cell Implantation Is Clinically Feasible, But Will it Be Effective?

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Regenerative medicine is acquiring increasing experimental importance. Several different types of stem cell exist, both in embryonic and in adult (cardiac, bone marrow and muscle) tissue, capable of proliferating and producing mature functional differentiated cells in any of the many tissues in the body. This has opened up the possibility of obtaining myocardial and endothelial tissue to "repair" damaged or poorly functioning areas of the heart.

As a result of the development of numerous experimental studies, several questions have arisen which should be answered in the clinical setting. These questions include: What are the ideal stem cells? Which patients would benefit most from this technique? Should different stem cells be used for different situations? How many should be transplanted? What is the most suitable route and timing for transplantation?

The first clinical trials were already under way before experimental regenerative studies had found clear answers to many of these questions. Of the various types of stem cell, those derived from bone marrow appear to have a greater capacity to differentiate into heart muscle fiber or endothelial cells, at least so far. Consequently, bone marrow stem cells have been employed in different countries in most of the clinical trials reported over the last three years.[1-7]

Whereas stem cell implants from muscle tissue may be the cause of the ventricular tachycardia seen in some patients, who have required implantation of defibrillators, stem cell implantation from bone marrow has so far been reported to be safe. Reports have described the various procedures used (intra-coronary injection, percutaneous or surgical intramyocardial implantation), the absence of complications, the clinical improvement and the trend towards an improvement in perfusion, as evaluated by simple photon emission computerized tomography (SPECT),[1,2,4-7] as well as myocardial viability evaluated by positron emission tomography (PET),[3] and improvements in ventricular remodeling and systolic function, evaluated by echocardiography[1-4,6,7] and magnetic resonance.[5] Nevertheless, important caveats also exist: the number of patients included in the trials is low, follow-up only reached 12 months in one case, only 3 studies included a control group[2,3,6] and the indications were not uniform (Table 1). Whereas in four of these studies the procedure was indicated for patients with chronic, non-revascularizable heart disease,[1,5-7] 3 studies included patients whose implants were undertaken in necrotic[2,3] or perinecrotic[4] areas a few days after infarction. Furthermore, the control group selected was not always the most ideal, as is clearly manifested in the study by Strauer et al,[2] where four of the ten patients treated had anterior descending artery lesions versus none in the control group.

The first publications from centers in Spain are now appearing. The group from the Clínica Universitaria in Pamplona has reported their preliminary results with myocardial regeneration using autologous myoblasts surgically implanted in the necrotic zone of 10 patients with a history of myocardial infarction and left ventricular dysfunction.[8] PET showed a significant trend (P=.028) for increased uptake of fluorodeoxyglucose (myocardial viability) with no perfusion changes, as assessed by ammonium 3 months after the procedure. This issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA reports the preliminary experience of a multidisciplinary team from centers in Valladolid and Murcia.[9] The initial results for the first 5 patients after intra-coronary transplantation show the procedure to be safe and feasible. The patients had an anterior acute myocardial infarction due to a single lesion of the left descending artery repaired by angioplasty. Patients received an intra-coronary infusion of bone marrow-derived cells 10-15 days after the infarction. No cardiac complications or arrhythmias were detected during the 6-month follow-up by dobutamine echocardiography, magnetic resonance studies and ECG Holter monitoring. As expected from this small series, no statistically signifi-

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TABLE 1. **Clinical Studies Using Bone Marrow Stem Cells***

Auttor and reference	Technique	N	Indication	EF pre, %	Follow-up							
					Months	Erg.	Echo	Isot. V.	MR	Catheterization	SPECT	PET
Hamano et al[1]	Surgical intra-l myocardia implantation	5	Non-revascularizable IHD		12		Yes			Right	^{201}Tl ^{99m}Tc	
Strauer et al[2]	Intra-coronary	10	Post-AMI	57±8	3		Dobutamine	Yes		Right	^{201}Tl red-reiny	
Assmus et al[3]	Intra-coronary	20	Post-AMI	52±10	4		Dobutamine			Angiography		FDG
Stamm et al[4]	Surgical intra-myocardial implantation	6	Post-AMI	21-47	9		Yes			Angiography	^{201}Tl	
Tse et al[5]	Percutaneous intra-myocardial implantation	8	Non-revascularizable IHD	58±10	3				Yes		^{99}mTc	
Perin et al[6]	Percutaneous intra-myocardial implantation	11	Non-revascularizable IHD	30±6	4	Yes	Yes			Angiography	^{99}mTc	
Fuchs et al[7]	Percutaneous intra-myocardial implantation	10	Non-revascularizable IHD	47±10	3	Yes	Yes			Adenosine	^{201}Tl/^{99}mTc	

*Angio. indicates coronary angiography, IHD, ischemic heart disease, Erg., ergometry, FDG, fluorodeoxyglucose; EF pre, ejection fraction before treatment, SVI, stroke volume index; SPET, single photon emission tomography; Tc, technetium; Tl, thallium; Isot. V., isotopic ventriculography; ESV, end-systolic volume.

cant functional improvement was seen, although in three patients the end-systolic volume tended to decrease and the ejection fraction tended to improve. As the authors conclude, stem cell transplantation in patients after an acute myocardial infarction "seems" to be safe and feasible and "might" lead to favorable remodeling.

This is precisely the same conclusion reached in previously reported clinical trials. All agree that myocardial regeneration in the clinical setting has only just begun, and that larger series are required using a similar methodology to that adopted in clinical trials of drugs to show that myocardial regenerative therapy, besides being a safe and feasible procedure, is also an efficient technique.

Non-invasive studies will assume a fundamental role in the follow-up of any possible improvement in perfusion, myocardial viability and contractile function of the areas treated. This is particularly difficult when these techniques are indicated during the subacute phase in patients with a myocardial infarction, as left ventricular systolic function and residual ischemia are parameters which can change spontaneously during the first few months after an infarction. Experimental studies have demonstrated the potential reversibility of these abnormalities in myocardial contraction after coronary obstruction, and radionuclide ventriculography with isotopes has shown that the left ventricular ejection fraction may improve in 24%-41% of patients between the first and tenth day after an acute myocardial infarction. Most studies comparing left ventricular systolic function before hospital discharge with that 6 months later have also shown a significant increase in ejection fraction. The fact that no significant differences in the ejection fraction values have been detected between the third and sixth months after the infarction support the suggestion that most of these changes occur during the first 3 months after an acute myocardial infarction.

Gated SPECT is a very suitable technique for undertaking this follow-up. Besides enabling evaluation of perfusion, function and viability, it is highly reliable for the assessment of ventricular volume and left ventricular ejection fraction. This technique has shown that slightly more than half the patients with an inferolateral infarction and 28% of those with anterior infarctions have an increase in the ejection fraction of greater than 5% between the first measurement, prior to hospital discharge, and 12 months later. These improvements were not accounted for by thrombolytic therapy, primary angioplasty or treatment with angiotensin converting enzyme inhibitors.[10] This functional improvement in non-revascularized patients, seen between the scans performed during the acute or subacute phase and those undertaken in the chronic phase, usually parallels improved myocardial perfusion.[10] It has been suggested that this improvement is due to spontaneous repermeabilization of the damaged artery or recovery of the microcirculation or cellular function after the ischemic phase and reperfusion. Indeed, the proportion of perfusion defects seen with thalium-201 in those patients who are treated conservatively after an acute

Course
Improved perfusion in 3/5 patients
Improved perfusion (*P*=.016), SVI (*P*=.01), ESV (*P*=.011), and SBP/SVI (P=.005) Improved flow reserve (*P*<.001), viability (*P* ≤.01), ESV (*P*=.01), and EF (*P*=.003) Improved perfusion in 5/6 and EF in 4/6 patients
Improved perfusion (*P*=.004), contractility (*P*=.008), and regional thickening (*P*=.004)
Improved perfusion (*P*=.02), ESV (*P*=.03), and EF (*P*=.03)
Improved perfusion (*P*<.001)

N, number of patients; PET, positron emission tomography; SBP, systolic blood pressure;

myocardial infarction is reduced with time. The extension of the perfusion defects has been shown to decrease between 18-48 hours and 6-14 days in patients with a reperfused infarction, and several researchers have attributed this recovery to the spontaneous development of collateral circulation and the recovery of microcirculation or transitory disorders in cell function, which contribute to radiotracer uptake. This spontaneous favorable course in perfusion and ventricular function in some patients after an acute myocardial infarction makes evaluation of the results of stem cell transplantation especially difficult to interpret in this type of patient.

Histological follow-up methods of transplanted stem cells undertaken so far in animal models are neither applicable nor recommended in humans. Clinical studies would benefit from a non-invasive method, which besides evaluating possible functional effects, would permit the stem cells to be tracked and their site of implantation documented. PET, SPECT, and magnetic resonance could in the future provide important advances in this field. Different molecular imaging techniques are currently being developed to follow the differentiation and engraftment of stem cells in the myocardium.

At the present time, we should be thankful that pioneering groups in Spain are undertaking the clinical evaluation of the results of this type of regenerative medicine. Their initial results suggest that stem cell transplantation is feasible and clinically safe. Nevertheless, we are still not in a position to provide a solid answer, based on scientific evidence, to the question of whether stem cell transplantation will be effective.

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