Review Article

Autologous Stem Cell Transplantation for Regeneration of Infarcted Myocardium: Clinical Trials

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Stem cells, or progenitor cells, are undifferentiated human cells that have the ability to produce the types of cell that exist in their anatomical surroundings (homing, transdifferentiation).[1-3] In this way they can develop into different cellular types and regenerate damaged tissue. In human bone marrow, stem cells replace more than one million red blood cells every day. Stem cells were recognised and isolated for the first time in 1997, when it was determined that in the healthy human neovascularisation could occur after the neonatal period.[1] Stem cells were initially identified in embryonic tissues, but recent data have demonstrated their presence in adult tissues, too, where their main function is cell renewal after tissue injury, illness, or ageing.[4,5]

There are three basic categories of pluripotent stem cells: a) embryonic stem cells;[6] b) bone marrow stem cells;[2,3] and c) tissue-specific stem cells, such as fibroblasts and myoblasts.[7] In the human body there are 200 trillion cells and 200 types of cell. To date, in humans about 20-30 types of stem cell have been identified. They are usually differentiated by the expression of surface antigen markers: *haemopoietic* stem cells, which are characterised mainly by the expression of surface marker $CD34^+$;[8] *mesenchymal* stem cells, which contribute to the regeneration of bones, ligaments, muscles, tendons, and fatty and connective tissue;[9] and *endothelial* stem cells, which are characterised by the expression of the surface markers $CD133^+$ and $CD34^+$ and contribute to the regeneration of the endothelium.[10]

Role of stem cells in myocardial regeneration

The interest of clinical cardiologists in stem cells developed recently, when it was shown that these cells could contribute to the regeneration of infarcted myocardium.[4,5] Indeed, myocardial cells show mitotic activity after a myocardial infarction, which means that the heart is not a post-mitotic organ.[11] A further indication of the active role of these cells was given by the detection of Y chromosomes in the myocardium of female patients who had undergone bone marrow transplantation from a male donor.[12] In healthy men, the levels of endothelial progenitor cells are a biological index of vascular function and cardiovascular risk.[13] Recently, specialised stem cells have also been detected in the myocardium, where they have the capability of regenerating myocardial tissue.[14]

Bone marrow stem cells, skeletal myoblasts, and embryonic cells have been used in experimental and clinical studies for the regeneration of infarcted myocardium. Skeletal myoblasts were the first

cells used for the regeneration of infarcted myocardium in humans. However, the initial encouraging results were overshadowed by indications that this type of therapy could have proarrhythmic complications. Early clinical studies showed that the incidence of sustained ventricular arrhythmias was of the order of 40%,[15,16] although in later studies the percentage was smaller.[17,18] The precise mechanism of the arrhythmia is unknown, but it may be related to the lack of a gap junctional coupling between myoblasts and endogenous myocardial cells that prevents the electrical integration of implanted cells.[19] Thus, implanted myoblasts survive as isolated islands, impeding propagation of the stimulus, slowing conduction, and causing re-entrant arrhythmias.

Embryonic stem cells were the first progenitor cells to be discovered.[20] They are the only totipotent cells and this property makes them especially attractive for such applications. They have been tested in the regeneration of myocardial tissue and pacemaker cells under experimental conditions.[21-23] Associated problems are their low rate of differentiation into cardiac myocytes and the possibility of causing neoplasms (teratomas).[24]

Cell types and delivery methods

Most studies to date have used implantation of whole bone marrow or mainly endothelial stem cells, which promote neovascularisation in the infarcted region:

1. Mononuclear whole bone marrow cells *ex vivo*[25] or after overnight cultivation,[26] which include both myocardial and endothelial progenitor cells, but in a small proportion.

2. Enriched $CD133^+$ cells,[27] which contribute to revascularisation but cannot regenerate myocardial tissue.

3. A heterogeneous population of cells originating from the peripheral blood, considered to be highly enriched with endothelial progenitor cells.[28] In this case, if the implanted cells are really endothelial progenitors they will be able to accelerate revascularisation but not to regenerate myocardial cells.

4. Another approach is the administration of cells after cultivation of bone marrow for several days, so as to develop a sufficient number of mesenchymal cells while maintaining the original number of endothelial cells.[29,30]

Mesenchymal cells are a particularly interesting type of progenitor cell whose differentiation capabilities have been recognised since 1999.[9] These cells are found mainly in the bone marrow and represent about 0.01% of the mononuclear cell fraction.[9] They can proliferate exclusively *in vitro* without apparent ageing or loss of their differentiation potential[31] and their ability to colonise the myocardium[32] and to differentiate into myocardial cells[33] has been proven.

Neovascularisation in adults depends mainly on endothelial stem cells. There is growing evidence that endothelial stem cells are found mainly in the $CD133^+$ cell fraction.[34] Apart from promoting vascularisation, an *in vitro* study has shown that endothelial stem cells are able to differentiate into myocardial cells.[35] However, more recent evidence rules out the possibility that endothelial stem cells can differentiate into myocardial cells *in vivo*.[36,37] Recently, there have been significant indications that mesenchymal stem cells do not increase the susceptibility to action potentials in myocardial cells that survive in the zone between healthy and infarcted myocardium. Human mesenchymal cells can express all three cardiac connective proteins (connexins 40, 43 and 45) and can form functional gap junctions with myocardial cells.[38,39] Mesenchymal stem cells create an electrical coupling with the living myocardial cells and this action reduces the likelihood of re-entry at the borders of the infarcted region.[40] In fact, three published clinical studies of transplanted mesenchymal cells have indicated a reduction in ventricular arrhythmias.[29,30,41] Furthermore, assessment of five patients who already had a defibrillator before stem cell implantation, in a study from our laboratory, showed no increase in arrhythmic activity during the two years after transplantation.[42]

As far as the transplantation method is concerned, three strategies have been described for implanting autologous bone marrow cells in human myocardium: epicardial implantation during cardiac surgical procedures;[25,27] endomyocardial implantation within the left ventricle using electroanatomical techniques;[43] and intracoronary implantation using a method similar to angioplasty.[26,28] Although the intracoronary approach is technically the easiest, less than 5% of implanted cells finally remain with the infarcted myocardium after intracoronary administration.[44] Endomyocardial implantation allows direct access to peri-infarcted regions, which theoretically have the best chance of regeneration; on the other hand, endomyocardial implantation of mesenchymal cells can create isolated tissue structures within the myocardium.[45]

Clinical trials

The use of autologous bone marrow stem cells has

had the widest application in clinical studies of regeneration of infarcted myocardium. The studies published to date are shown in Table 1. It is apparent from the table that the most common transplantation method is intracoronary delivery, while most researchers have used cultured bone marrow cells. Table 2 shows the randomised, controlled trials from which conclusions may be drawn concerning the efficacy of the method. It is interesting that five studies were unable to show any beneficial effect. In addition, the mode of action of the cells has not yet been determined and does not appear to involve significant regeneration of myocardial tissue. Suggested mechanisms include induction of neovascularisation, remodelling of the connective tissue that forms the chronic scarring, further mobilisation of a larger number of similar cells from the bone marrow, and paracrine effects.[46,47,77]

The safety of the use of bone marrow stem cells has been satisfactorily proven. These cells do not appear to be arrhythmogenic, though some reports have raised the possibility of calcified foci within the myocardium following grafting.[45] Of course, the safety of any new method requires long-term monitoring of the patients concerned before definite conclusions can be drawn.

Conclusions

Regeneration of infarcted myocardium using autologous stem cells in humans is a new strategy for the

Table 1. Clinical studies of stem cell administration for the regeneration of infarcted myocardium.

Study	Patients	Cell type	Mode of delivery
Stamm[27]	12	BMC	Open heart/epicardial
Li[48]	70	CPC (GCSF)	Open heart/epicardial
Galiñanes[49]	14	BMC	Open heart/epicardial
Hendrikx[50]	20	BMC	Open heart/epicardial
Ozbaran[51]	6	GCSF-mobilised CPC	Open heart/epicardial
Pompilio[52]	4	GCSF-mobilised AC133$^+$	Open heart/epicardial
Tse[25]	8	BMC	Endomyocardial
Perin[43]	14	BMC	Endomyocardial
Fuchs[53]	10	BMC	Endomyocardial
Losordo[54]	24	GCSF-mobilised CD34$^+$	Endomyocardial
Strauer[26]	10	BMC	Intracoronary
REPAIR-AMI[55]	204	BMC	Intracoronary
ASTAMI[56]	100	BMC	Intracoronary
BOOST[57]	60	BMC	Intracoronary
Fernández-Avilés[58]	20	BMC	Intracoronary
IACT study[59]	18	BMC	Intracoronary
Meluzín[60]	60	BMC	Intracoronary
TCT-STAMI[61]	20	BMC	Intracoronary
Ruan[62]	20	BMC	Intracoronary
TOPCARE-AMI[63]	59	BMC/CPC	Intracoronary/subcutaneous
TOPCARE-CHD[64]	75	BMC/CPC	Intracoronary
MAGIC cell[65]	27	CPC(GCSF)/GCSF	Intracoronary/subcutaneous
MAGIC Cell-3-DES[66]	96	BMC/GCSF	Intracoronary
Katritsis[29]	11	MSC+EPC	Intracoronary
Chen[30]	69	MSC	Intracoronary
Bartunek[68]	19	EPC (CD133$^+$)	Intracoronary
Manginas[69]	12	EPC (CD133$^+$,133$^-$,34$^+$)	Intracoronary
Li[70]	70	GCSF-mobilised CPC	Intracoronary
Erbs[71]	26	CPC (GCSF)	Intracoronary
Boyle[72]	5	GCSF-mobilised CD34$^+$	Intracoronary
Janssens[73]	67	BMC	Intracoronary
PROVACEL[41]	53	MSC	Intravenous
FIRSTLINE-AMI[74]	30	GCSF	Subcutaneous
REVIVAL-2[75]	114	GCSF	Subcutaneous
STEMMI[76]	62	GCSF	Subcutaneous

BMC – bone marrow stem cells; CPC – circulating progenitor cells; EPC – endothelial progenitor cells; GCSF – granulocyte colony-stimulating factor; MSC – mesenchymal cells.

Table 2. Randomised, controlled trials of stem cell administration for the regeneration of infarcted myocardium.

Study	Patients	Cell type	Mode of delivery	Endpoint	p	Follow up (months)
MAGIC cell[65]	27	CPC(GCSF)/GCSF	IC/SC	LVEF	0.005	6
Chen[30]	69	MSC	IC	LVEF	0.01	3
TOPCARE-AMI[63]	59	BMC/CPC	IC/SC	LVEF	<0.001	12
FIRSTLINE-AMI[74]	30	GCSF	SC	LVEF	<0.003	12
REPAIR-AMI[55]	204	BMC	IC	Clinical events	0.006	12
TOPCARE-CHD[64]	75	BMC/CPC	IC	LVEF	<0.001	3
Erbs[71]	26	CPC (GCSF)	IC	Infarct size	<0.05	3
ASTAMI[56]	100	BMC	IC	Infarct size	0.07	6
BOOST[57]	60	BMC	IC	LVEF	0.27	18
Janssens[73]	67	BMC	IC	LVEF	0.36	4
REVIVAL-2[75]	114	GCSF	SC	Infarct size	0.56	4-6
STEMMI[76]	62	GCSF	SC	LVEF	0.7	6
PROVACEL[41]	53	MSC	IV	LVEF	0.04	6
Losordo[54]	24	$CD34^+$ (GCSF)	IM	SPECT	-	6
MAGIC Cell-3-DES[66]	96	BMC/GCSF	IC	LVEF	<0.05	6
TCT-STAMI[61]	20	BMC	IC	LVEF	<0.05	6
Meluzín[60]	60	BMC	IC	LVEF	0.027	3
Ruan[62]	20	BMC	IC	LVEF	<0.05	6
Hendrikx[50]	20	BMC	EC	LVEF	0.23	4
Li[48]	70	CPC (GCSF)	IC	LVEF	0.041	6
Tse[67]	28	BMC	IM	LVEF	0.044	6

EC – epicardial; IC – intracoronary; IM – intramuscular; IV – intravenous; LVEF – left ventricular ejection fraction; SC – subcutaneous; SPECT – single photon emission computed tomography. Other abbreviations as in Table 1.

treatment of patients with myocardial infarction and possible heart failure. The clinical trials published to date suggest, but do not prove, a clear improvement in infarcted myocardium as a result of this technique. The method appears to be clinically safe, but many questions still remain unanswered regarding the mode of action of this therapy, the ideal way of delivery, the most effective types of cell, and the patient populations who are most likely to benefit from this treatment.

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