# Stem cell therapy for acute myocardial infarction and subsequent heart failure

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## Abstract

Transplantation of stem cells in the heart has emerged as a potential strategy in patients with acute myocardial infarction and cardiac insufficiency following ischaemic heart failure. The present stage of knowledge suggests that the use of skeletal myoblasts or autologous stem cells is a safe, feasible and effective therapy. The available data suggest the benefit of using myoblasts in cardiac function, increasing the left ventricular ejection fraction and decreasing the end diastolic and end systolic volumes. An increase in contractility of the ischaemic area, a decrease in functional NYHA class and a decrease in the number of revascularization procedures and hospitalizations are also envisaged. Although the mechanisms involved are still not known, suggested hypotheses are cell differentiation into myocites, the promotion of angiogenesis, the release of paracrine factors that increase the function of the surviving myocites or those responsible for mobilization of the stem cells in the heart, inhibition of extracellular matrix destruction with a decrease in apoptosis of the cardiomyocites, and fusion between the transplanted cells and resident myocytes.

It is important to emphasize that neither the best place to collect stem cells, nor the best way of administering them, have yet been determined.

There are also some issues that have yet to be resolved concerning the technical difficulties and possible complications. Hopefully, research currently underway will clarify these doubts and enable us to reach more reliable conclusions.


Key words: stem cells, acute myocardial infarction, heart failure, myoblasts, ventricular remodeling.

## INTRODUCTION

In recent years, research on stem cells has progressed rapidly, suggesting a possible broad spectrum of applications of these cells, particularly in hematology malignancies, solid tumors, metabolic diseases, transplantation, and diseases of the immune system.

Cardiology is also interested in these new techniques, and investigation into the use of these cells in acute myocardial infarction (AMI) and subsequent congestive heart failure (CHF) began sixteen years ago[1] in laboratory animals. Phase I and II clinical trials have been conducted for the last five years[2].

Following AMI, primary changes occur, consisting of necrosis and apoptosis of myocytes and loss of extracellular matrix. Reabsorption of necrotic tissue is done by macrophages and neutrophils. A phase of proliferation of fibroblasts and collagen deposition then occurs, with the formation of fibrous tissue.

Secondary changes that lead to ventricular remodeling depend on the infarction area (occurring particularly in apical and anterior transmural infarctions), the healing process, and the stress to which the ventricular wall is subjected.

The deposition of fibrous tissue leads to sliding of the muscle fibers with their consequent distension. This distension is still present in 30% of patients up to three months after AMI, and can lead to complications, such as aneurysm, rupture of the left ventricle (LV) and heart failure (HF). Creatine kinase (CK) has been used as a marker of this process, and the end systolic volume (ESV) as a marker of mortality.[3,4]

Given that AMI is one of the main causes of HF, the use of stem cells opens up new therapeutic perspectives.[5] The following techniques have been used: hematopoietic stem cells (HSC) from bone marrow (BM), with direct aspiration; HSC from BM mobilized into the peripheral blood using G-CSF (growth colony stimulating factor) or SCF (stem cell factor);[2,6] and biopsy-derived striated muscle myoblasts (MB).

Despite the success achieved so far, the mechanisms of action of the cells used are unknown, with cell differentiation into myocytes,[7-11] promotion of angiogenesis[11] and release of paracrine factors, such as IGF-1 (Insulin Growth Factor) that increase the function of the surviving myocytes, being proposed as possible mechanisms.[12,9] Another possible process is the secretion of paracrine factors, which increases

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the mobilization of stem cells in the heart. [7,9] The inhibition of extracellular matrix destruction with decreased apoptosis of cardiomyocytes, and fusion between the transplanted cells and resident myocytes, may also be observed.[9]

Studies have focused on the use of G-CSF (Granulocyte Colony Stimulating Factor), the use of myoblasts, and the use of autologous stem cells from bone marrow in ischemic heart disease.

## G-CSF IN AMI

In the FIRSTLINE-AMI[13] trial, it was found that twelve months after treatment of post-MI patients with G-CSF, the left ventricular ejection fraction (LVEF) increased (from 48±4% to 54±8% after four months, p<0.005 and to 56±9% after twelve months, p<0.003), as did the thickness of post-infarct myocardium (from 1.16±0.29mm, p<0.05 vs. control to 1.20±0.28mm after 12 months, p<0.001). No inflammation, restenosis, or other adverse effects were observed.

Ohtsuka[4] demonstrated that there is no difference in the improvement of cardiac function when G-CSF or G-CSF+SCF was administered to myocardial-infarcted rats; however, a higher number of capillaries was observed when G-CSF was administered in isolation, suggesting that this factor induces neovascularisation, preventing myocyte apoptosis and ventricular dilation. This induction of angiogenesis was confirmed by Ohki et al.[14] who demonstrated that after administration of G-CSF, there is mobilization of the VEGF (vascular endothelial growth factor) secreting neutrophils to the ischemic site, with targeting of the endothelial progenitor cells from bone marrow (BM) VEGFR1+ cells and hematopoietic cells from BM VEGFR2+ to the site, the former being responsible for the increased number of vessels.

Engelmann[15] confirmed the increase of myocardial perfusion induced by treatment with G-CSF. However, this factor did not prove beneficial when administered belatedly (31±24h after successful revascularization): the increase in LVEF after three months was 6.2±9.0% when G-CSF was used vs. 5.3±9.8% when placebo was used, p=0.77.

In the MAGIC trial,[16-17] which was divided into two phases – the first lasting six months and the second lasting twenty-four months – the results were compared for the groups using stem cells mobilized with G-CSF, G-CSF alone, or the control procedure.

After six months, a greater increase in LVEF (+6.2±3.6% vs. -4.3%±10.1%, p=0.004) and a greater decline in ESV (-15.7±13.0 vs. +0.3±16.7mL, p=0.075, without statistical significance) were observed in the mobilized cell group, compared with the group that received G-CSF only.

These results were also observed at the end of two years: LVEF 58.9±9.9%, p<0.01 compared with the baseline and ESV 46.9±20.0ml, p<0.05 compared with the baseline in the group of mobilized cells, LVEF 53.1±12.8%, p=0.077 and ESV 67.9±44.2mL, p=0.043 in the group with G-CSF only.

However, it was found that the difference in improvement of cardiac function obtained with the infusion of stem cells mobilized with G-CSF vs. control was not statistically significant. The variation in LVEF at the end of two years was +9.0±5.5% vs. +7.7±6.8%, p=0.682, respectively. This result can be explained by the small sample size.

In addition, there was not a significant difference between LVEF in the G-CSF group vs. control (ŘLVEF at two years: +2.6±7.3% vs. +7.7±6.8%, p=0.207).

Due to the possibility of restenosis,[14] Jorgensen et al[6] conducted a study which showed no difference in intimal hyperplasia in patients treated with G-CSF or placebo (1.87±1.41 and 1.89±1.39, p=0.97).

By contrast, in the MAGIC trial,[16,17] the rate of restenosis was higher in the patients who received G-CSF.

In the meta-analysis of Zohlnhofer et al,[18] the use of G-CSF in patients with AMI showed no benefit. No improvement was observed in ventricular function (p=0.36), neither was there a reduction in ischemic area in the patients treated with G-CSF (p=0.17).

## MYOBLASTS

Myoblasts (MB) are quiescent, ischemia-resistant stem cells that reside beneath the basal membrane of striated muscles. They can be easily isolated by muscle biopsy, and easily expanded in culture medium. They group together to form *in vitro* and *in vivo* myotubes, producing SDF-1 (stromal cell-derived factor-1), HGF (hepatocyte growth factor) and VEGF, mobilizing hematopoietic stem cells.[2,19]

### Protocol for MB transplant:

The protocol for MB transplant establishes inclusion and exclusion criteria; it uses electromechanical mapping with NOGA catheter, angiography, echocardiography and magnetic resonance imaging; it addresses

the need for biopsy of the thigh muscle and expansion in cell culture medium, and procedure for the direct injection of myoblasts in the infarcted area.

In cases of AMI, parameters are established that should be followed, where applicable, for the maintenance therapy (aspirin, ACE inhibitors; beta blockers, statins, clopidogrel + revascularization procedure), and guidelines for monitoring adverse reactions, particularly arrhythmias (possible use of prophylactic amiodarone).

Follow-up was carried out through clinical, laboratory and imaging of myocardial perfusion (coronary angiography and left ventricular angiography, dobutamine stress echocardiography, cardiac perfusion imaging, and cardiovascular MRI).

## Myoblasts in Acute Ischemia

Dowell[20,11] concluded that the myoblasts could be safely transplanted, and that this results in improved cardiac function, suggesting angiogenesis as the mechanism responsible.

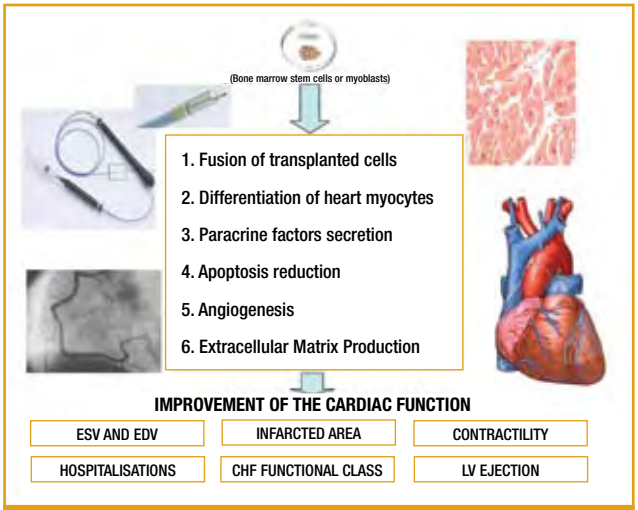
Hagège[21,12] suggest that the myoblasts are transformed into myotubes[22] and maintain their contractile skeletal muscle properties, since the immunohistochemical analysis of the graft was negative for connexin 43, desmosome and pan-cadherin[21,22] and positive for troponin T and CD56, suggesting an unknown paracrine action as its mechanism.

The absence of electromechanical coupling between the graft and cardiomyocytes was demonstrated.[22]

## Myoblasts in Chronic Heart Failure following AMI

Menasché et al[23] observed, in their study, an increase in thickness of the remaining post-infarction myocardium after 10.9 months, and several episodes of ventricular tachycardia (VT). They suggest heterogeneous distribution of gap junctions due to the presence of the graft; cardiomyocyte necrosis by direct action of the syringe in the myocardium with release of arrhythmogenic products; and formation of re-entries at the edges of the ischemic area, as mechanisms of arrhythmia.

Smits[24] also found increased thickness of post-infarction myocardium (0.9±2.3mm baseline vs. 1.8±2.4mm after three months, p=0.008) and an increase in LVEF after six months (baseline from 36±11% to 41±9% after three months, p=0.009 and




Possible benefits on the cardiac function of stem cells or myoblasts therapy. Adapted from available pictures in the Internet.

FIG. 1

to 45±8%, p=0.23 without statistical significance after six months).

Siminiak[25] used the transcoronary route as the delivery protocol, obtaining an improvement in LVEF, NYHA (New York Heart Association) functional class, and passage of segments from akinetic to hypokinetic.

Hagège's longest clinical trial[1] lasted fifty-two months, after which the author concluded there was an increase in LVEF (24.3±4% to 31±4.1%, p=0.001), an improvement in functional class of HF (2.5±0.5 to 1.8±0.4, p=0.004) and a decrease in the number of hospitalizations.

Instead of using isolated myoblasts, Memon et al[19] transplanted myoblast layers, canceling the disruption of extracellular matrix. The results, after eight weeks, were increased cellularity, increased angiogenesis, reduced fibrosis and increased recruitment of SDF-1, HGF and VEGF producing hematopoietic cells (p=0.05).

## STEM CELLS FROM BONE MARROW

Stem cells from non-fractionated BM include populations of differentiated cells, hematopoietic stem cells capable of differentiating into cardiomyocytes, endothelium and smooth muscle cells,[26] endothelial progenitor cells capable of differentiating into myocytes,[26] hemangioblasts capable of producing new vessels,[26]

**TABLE I**

**Comparing the results obtained in the different stages of the MAGIC study**

| LVEF (%) | Stem cells | P value compared to the baseline | G-CSF | Control | P value compared to the baseline |
|---|---|---|---|---|---|
| Baseline | 48,9±9,0 | | 53,0±14,3 | 44,4±9,2 | |
| 6 months | 55,1±7,4 | <0,01 | 48,7±11 | 50,3±8,4 | <0,01 |
| 12 months | 57,4±6,8 | <0,01 | 53,1±11,3 | 49,9±11,6 | <0,05 |
| 24 months | 58,9±9,9 | <0,01 | 53,1±12,8 | 51,3±9,4 | <0,01 |

| VTDVE (mL) | Stem cells | P value compared to the baseline | G-CSF | Control | P value compared to the baseline |
|---|---|---|---|---|---|
| Baseline | 133,0±34,8 | | 124,2±33,5 | 145,5±50,6 | |
| 6 months | 117,4±37,9 | <0,05 | 115,9±44,3 | 134,3±49,2 | |
| 12 months | 109,5±33,5 | <0,05 | 125,2±43,6 | 125,5±45,2 | <0,05 |
| 24 months | 111,7±37,7 | | 134,6±50,0 | 126,8±44,4 | <0,05 |

| VTSVE (mL) | Stem cells | P value compared to the baseline | G-CSF | Control | P value compared to the baseline |
|---|---|---|---|---|---|
| Baseline | 70,3±28,9 | | 61,8±35,8 | 81,2±38,0 | |
| 6 months | 54,6±23,7 | <0,01 | 62,1±37,9 | 66,7±33,4 | <0,05 |
| 12 months | 48,4±19,3 | <0,01 | 62,8±40,4 | 65,8±35,2 | <0,05 |
| 24 months | 46,9±20,0 | <0,05 | 67,9±44,2 | 63,7±34,4 | <0,05 |

and mesenchymal stem cells capable of differentiating into fibroblasts and cardiomyocytes.

Their use requires invasive procedures, and their expansion *in vitro* is not possible.

### Basic protocol for stem cells from bone marrow:

For the injection of stem cells from bone marrow, the protocol establishes the corresponding inclusion and exclusion criteria; outlines procedures to be complied with in bone marrow aspiration from the iliac crest and the isolation of mononuclear cells CD34+, AC133+ using the Ficoll protocol; sets criteria for parallel microbiological studies on aspirated bone marrow and transplantation of cells through the insertion of a balloon catheter in the accessed vessel; and addresses percutaneous angioplasty with prolonged contact time to allow cell migration, preventing migration to other organs.

In cases of AMI, the protocol establishes the standard therapy, where applicable. It also reports the follow up procedures through monitoring of cardiac function.

### Stem Cells from Bone Marrow in AMI

In the first trial by Strauer,[26] the tendency was towards a reduction in the ischemic region (30±13 to 12±7%, p=0.005), a 26% decrease in perfusion defect (from 174±99 to 128±71cm2, p=0.016) and increase in LVEF (57±8 to 62±10%, p=NS), without statistical significance. Also, an increase in ejection volume (49±7 to 56±7mL/m2, p=0.010) was observed, as well as a decrease in the end systolic volume (from 158±20 to 143±30mL, p=NS), though the latter was without

**TABLE II**

**Comparative results on Smits and Hagège studies**

| | Smits | Hagège |
|---|---|---|
| LVEF (%) | 36±11 para 45±8, p=0,23 | 24,3±4para28,7±8,1, p=0,001 |
| NYHA | — | 2,5±0,5para1,7±0,5, p=0,004 |

statistical significance. Increased contractility was also observed at the end of three months (2.0±1.1 to 4.0±2.6cm/s, p=0.028).

In the TOPCARE-AMI trial[27], twenty patients who had undergone reperfusion therapy following AMI, with stem cells derived from the bone marrow (n=9) or circulating in the peripheral blood (n=11), underwent transplant.

No significant differences were observed in any of the baseline parameters between the patients who received blood-derived or bone marrow-derived stem cells.

At the end of four months, an increase was obtained in LVEF (51.6±9.6% to 60.1±8.6%, p=0.003 in the group receiving therapy vs. 51±10 to 53.5±7.9 %, p=NS in the control group) and increased motility of the infarcted wall (-1.5±0.2 to -0.5±0.7, p<0.001 in the group receiving therapy).

A decrease in ESV was observed (56.1±20mL to 42.2±15.1mL, p=0.01 in the group receiving therapy vs. 50.4±17.5 to 58.2±32.2mL, p=NS in the control group), and a decrease in EDV (117.2±35.1 to 105.2±29.9, p=0.199 in the group receiving therapy vs. 102±23.6 to 123±50.3mL, p=NS in the control group), but with the limitation that some of these results were not statistically significant, and an increase in coronary flow reserve (p<0.001) at the end of four months.

In the twelve-month follow-up of the TOPCARE-AMI trial[8], the improvement in cardiac function was compared with the use of circulating progenitor cells (n=30) and bone marrow-derived progenitor cells (n=29).

A tendency for LVEF to increase (50±10% to 58±10%, p<0.001) was observed, as well as a decrease in size of the infarction (39±15 to 21±17, p <0.001), a decrease in ESV (54±19ml to 44±20mL, p<0.001), and absence of reactive hypertrophy (the marginal zone of the infarction increased from -1.42±0.19 to -0.49±0.63 in both groups at the end of twelve months (p<0.001).

Stamm[28] found, at the end of nine months, increased left ventricular function and increased perfusion of the infarcted tissue.

Chen[29] also observed a decrease in the percentage of hypokinetic, akinetic and dyskinetic segments (13%±5 vs. 32±11%, p=0.01 after three months), an increase in contraction speed of the infarcted wall (2.17±1.3 to 4.2±2.5cm/s, p=0.01 at 3 months), increased LVEF (from 49±9 to 67±11%, p=0.01 at six months and 67±3%, p=0.01 at six months) and a decrease in end systolic volumes (from 76±18ml to 58±13ml at three months, p=0.01) and end diastolic volume (from 169±21ml to 131±19 at three months , p=0.01) at the end of three and six months.

In the REPAIR-AMI trial[30], a decrease in the need for revascularization procedures (p=0.01) and an increase in LVEF (5.5±7.3%, p=0.01, either higher or lower than its post-AMI value) were observed, but only in patients transplanted after four days of reperfusion.

In the first phase of the BOOST trial,[12] a 6.7% increase in LVEF was observed after six months (p=0.0026), when compared with the placebo group. In the second phase of that same trial, no increase in LVEF was observed when compared with the control group, at the end of eighteen months (p=0.27).

In the ASTAMI trial[11], no improvement in cardiac function was observed (using a 5% increase in LVEF as the criterion) at the end of the six month follow-up.

The results obtained by MRI (magnetic resonance imaging) at the end of six months showed no significant differences between groups. LVEF increased from 54.8±13.6 to 56.2±14.9%, p=0.054 in the BMC (Bone Marrow Cells) Group compared with an increase from 53.6±11.6 to 58.1±11.4%, p=0.054 in the control group. The EDV decreased from 161.7±46.3mL to 154.1±54.1mL, p=0.49 in the BMC group vs. 165.3±46.7 to 162.5±45.3mL, p=0.49 in the control group, though these values were without statistical significance. The infarcted area decreased from 22.0±12.8% to 20.9±11.5%, p=0.07 in the BMC group vs. 22.2±14.0 to 19.6±12.5%, p=0.07 in the control group.

Seeger[32] compared different protocols for isolation of BM mononuclear cells used in the REPAIR-AMI

**TABLE III**

**Comparing the results obtained through the studies of Strauer, TOPCARE-AMI, Chen, REPAIR-AMI, BOOST and ASTAMI**

| | Strauer et al | TOPCARE-AMI | Chen | REPAIR-AMI | BOOST | ASTAMI |
|---|---|---|---|---|---|---|
| LVEFi (%) | 57±8, p=NS | 50±10, p<0,001 | 49±9, p=0,20 | 48,3±9,2, p=0,31 | 50,0, p=0,0026 | 41,3±10,4, p=0,77 |
| LVEFf (%) | 62±10, p=NS | 58,3±10, p<0,001 | 67±3%p=0,01 | 53,8±10,2, p=0,31 | 56,7, p=0,0026 | 49,3±13,2, p=0,77 |
| ESVi (mL) | 82±26, p=0,011 | 54±19, p<0,001 | 76±18, p=0,01 | 67±26, p=0,09 | 43,0, p=0,33 | — |
| ESVf (mL) | 67±21, p=0,011 | 44±20, p<0,001 | 58±13, p=0,01 | 67±30, p=0,09 | 42,4, p=0,33 | — |
| VTDVEi (mL) | 158±20, p=NS | 111±29, p=0,45 | 169±21, p=0,01 | 128±38, p=0,09 | 84,2, p=0,32 | 162,3±59,1, p=0,74 |
| EDVf (mL) | 143±30, p=NS | 102±31, p=0,45 | 131±19, p=0,01 | 141±43, p=0,09 | 91,7, p=0,32 | 151,1±52,9, p=0,74 |

and ASTAMI trials. Using the Ficoll and Lymph prep protocols (of the REPAIR-AMI and ASTAMI trials, respectively), a smaller number of stem cells (19.1±7.6 vs. 25.5±13, p=0.027) was observed, as well as lower cell viability (4.4±3.6 vs. 6.8±4.8, p=0.043), lower number of CFU (colony forming units) (3891±2425 vs. 5270±3918, p=0.023), lower migration in response to the SDF-1 (822±501 vs. 2195±1287, p=0.02) and less neovascularisation in the ischemic limbs of rats (26±7.5 vs. 48±23, p=0.012) in the last trial referred to.

In the meta-analysis performed by Burt et al[33] and Martin-Rendon et al,[34] the use of stem cells in patients with acute myocardial infarction suggested a benefit when compared with conventional therapy. Further studies are needed, to improve the technique.

### Stem Cells from Bone Marrow in Chronic Cardiac Insufficiency following AMI.

Perin[35,36] found increased LVEF, decreased end systolic volume and increased kinetics in the infarcted wall at the end of four months after the transplantation.

Strauer[9] found, at the end of three months, a 30% decrease in the infarcted area (p=0.02), a 15% increase in LVEF 15% (p=0.02), a 57% increase in the rate of the infarcted wall (p=0.001) and a 15% increase in oxygen consumption in patients who underwent cell transplantation, compared with the control group.

## DISCUSSION AND CONCLUSION

Although the articles found in the literature focus on the relevance of this therapy and its safety, there remain some questions that have not been sufficiently clarified.

With regard to the protocol,[32] for example, the type of bone marrow-derived cells that is most effective in improving cardiac function and, therefore, which cells are more suitable for transplants, is not known.

It must be considered that during and up to the seventh day after AMI, an inflammatory condition is observed, which can lead to transplanted stem cell differentiation in inflammatory cells with subsequent exacerbation of the process.

Considering that the secretion of VEGF (Vascular Endothelial Growth Factor) reaches its peak on the seventh day, and the formation of capillaries, pericytes and endothelial bridges, and the fact that the muscle wall of the blood vessels (with a consequent decrease in permeability) is formed on the twenty-eight day (with no expansion of the scarring before the fourteenth day), the period between the seventh and fourteenth days is recommended as the best time for transplant.[5,26,29]

The technique of placing cells, ensuring that the widest possible number reaches the affected site, is also one of the issues on which there is no consensus.

The selective application by catheter into the reperfused artery,[5] which is a homogeneous technique,[5] preferred after an AMI due to high levels of VEGF and SDF-1 that facilitate the homing process, is not recommended in the application of myoblasts, as embolism and thrombosis may occur. Direct myocardial injection[37] is the treatment of choice in the ischemic aetiology of HF due to low levels of VEGF and SDF-1,

**TABLE IV**

**Results of the second TOPCARE-AMI study**

| Use of Circulating Stem Cells | | | |
|---|---|---|---|
| | **Baseline** | **4 months** | **P value** |
| LVEF (%) | 51±10 | 59±10 | p<0,001 |
| ESV (mL) | 107±26 | 109±33 | P=0,45 |
| EDV (mL) | 52±16 | 42±18 | p<0,001 |

| Use of Stem Cells from the Bone Marrow | | | |
|---|---|---|---|
| | **Baseline** | **4 months** | **P value** |
| LVEF (%) | 49±10 | 57±10 | p<0,001 |
| ESV (mL) | 111±29 | 109±27 | P=0,45 |
| EDV (mL) | 56±21 | 45±21 | p<0,001 |

and, as it is preferable for the use of myoblasts, there is a possibility of the formation of isolated islands of cells.

The most reliable technique seems to be direct myocardial injection through cardiothoracic surgery. However, given that this is the most invasive technique, its disadvantages should be taken into account.

Alternative methods are currently being investigated, particularly transvenous and transpericardial injection of cells.

Despite the encouraging results achieved so far, stem cell therapy can cause adverse effects, such as hypotension, arrhythmia, thrombosis, and neoplasm, and its risks/benefits should be evaluated on a case-by-case basis. The percentage of improvement in cardiac function that should be considered significant has yet to be defined.

Given the short period covered by the existing clinical trials (the maximum time was two years, in the MAGIC trial), the evolution of transplanted cells over time is ignored, with loss of cells being possible through mechanisms of cell death.[5]

Further research is needed, with more precise criteria, to evaluate the benefit of this type of therapy, as well as phase III and IV clinical trials that might answer important questions and prompt debate on emerging issues. Further trials are awaited, that will enable the morbidity and mortality associated with this therapy to be assessed.

New options for cell therapy are on the horizon, such as the use of genetic vectors capable of injecting new genetic information or altering the expression of certain genes in damaged or transplanted cells;[5] antiapoptotic treatments that reduce the level of apoptosis of damaged and transplanted cells,[5] co-injection of angiogenic factors to increase vascularisation, accelerating the healing process and increasing the capacity of proliferation of transplanted cells,[5] induction of ectopic expression of connexin 43, allowing electrical coupling of transplanted cells with cardiomyocytes;[5] methods to improve strategies of homing of transplanted cells;[5] the use of smooth muscle cells[37] that can modify the extracellular matrix, induce angiogenesis and improve cardiac function; and the activation of stem cells in the heart.[37]

The knowledge and research carried out to date do not allow the value of the new therapeutic approaches to properly assessed. It is therefore important to continue with the research, not closing doors that could, hopefully in the near future, bring valuable new tools and/or techniques that could replace existing therapies for AMI and IHF following AMI. ■

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