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Clinical trials with adult stem/progenitor cells for tissue repair: let's not overlook some essential precautions

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The medical community is currently experiencing a wave of enthusiasm for clinical trials in which adult stem/progenitor cells are used to repair tissues. The enthusiasm is based on promising results in animal models for a variety of diseases and the encouraging reports from some initial clinical trials.[1-6] It is also driven by the prospect that stem/progenitor cells may offer new hope for patients with end-stage diseases for which there are no therapies. In the wave of enthusiasm, however, several essential precautions are not being fully addressed. Therefore, there is a great danger that potentially important new therapies will be discarded prematurely because of poorly designed clinical trials.

In theory, adult stem/progenitor cells may provide a therapy for an almost unlimited number of serious and currently untreatable diseases. Their potential derives from their normal role as cells that repair injured tissues.[1,7] It is now known that essentially every tissue and organ in the body contains such cells for tissue repair. After the stem/progenitor cells in a tissue are exhausted by severe or chronic injury, they can be supplemented by similar cells that flow through the blood stream from the bone marrow. Both the stem/progenitor cells found in most tissues and the similar cells from bone marrow can differentiate into most cellular phenotypes and thereby replace damaged cells. It was recently made known, however, that the cells can repair injured tissues by a variety of other mechanisms, some of which are still poorly defined. The cells are a rich source of chemokines and cytokines, as is well known from the use of confluent layers of the stem/progenitor cells referred to as marrow stromal cells as feeder layers for culture of hematopoietic cells. The chemokines and cytokines can stimulate regeneration of cells by inhibiting apoptosis, suppressing immune reactions, and increasing angiogenesis. The cells can also enhance proliferation and differentiation of tissue-endogenous stem/progenitors cells as indicated by recent experiments in which human stem/progenitor cells were infused into the hippocampus of immunodeficient mice.[8] In addition, they may rescue cells with nonfunctioning mitochondria by transfer of either mitochondria or mitochondrial DNA, as was recently observed in coculture experiments.[9] To some extent, they may also repair tissues by cell fusion.[1,10] Recent observations, in fact, suggest that we may have unnecessarily confused ourselves by referring to them as adult stem cells. They can more properly be referred to as reparative cells, or some catchier name.

Despite the great promise, it is clear that development of new therapies with cells that repair tissues will not be a linear sequence of events. As with most dramatically new therapies, the data from basic studies and from animal models are never as conclusive as one would like. The best one can say is that the data are encouraging enough to justify carefully controlled trials in patients in whom the risks can be fully justified. The molecular events of tissue repair remain a mysterious and complex process, perhaps one of the most complex processes in all of biology and medicine. Therefore, as researchers proceed, the current clinical trials must be examined carefully and used as a basis for further research to improve the therapies. The situation is analogous to the development of bone marrow transplantation in which the first long-term successes[11] were not achieved until nearly a decade after the first trials in patients with end-stage hematologic malignancies.[12]

The first clinical trials with adult stem/progenitor cells to repair nonhematopoietic tissues were carried out with the plastic adherent cells from bone marrow referred to in the hematologic literature as marrow stromal cells, but first defined as fibroblastoid colony-forming units, then as mesenchymal stem cells, or most recently as multipotent mesenchymal stromal cells (MSCs).[1,13] The cells can readily be isolated from a small sample of marrow and rapidly expanded so as to generate large numbers of cells for autologous therapies. The initial clinical trials with MSCs were in patients with severe osteogenesis imperfecta[2] and then in patients with mucopolysaccharidoses.[3] Subsequently, trials were initiated for graft-versus-host disease that capitalize on the ability of the cells to suppress immune reactions.[4,5]

Currently, the largest number of clinical trials is in patients with heart disease. Here, a confusing variety of cells and strategies for different syndromes have been tested (Table 1).[14-43] One approach was to mobilize bone marrow cells by subcutaneous administration of G-CSF. Another was to isolate unfractionated mononuclear cells from autologous bone marrow and infuse the cells either into a coronary artery or into the border region of myocardial infarcts. Still another approach was to isolate $CD34^+$ or $CD133^+$ cells from marrow or $CD34^+$-enriched cells from peripheral blood after mobilization and then to infuse the cells into a coronary artery or the borderline of infarcted areas. Still other approaches were to use the same routes of infusion with either isolated endothelial progenitor cells or MSCs. To date, only a limited number of adverse effects have been attributed to any of the different therapies. In contrast, an earlier trial in which skeletal myoblasts were infused into the myocardium produced a high incidence of arrhythmias. Most of the trials using bone marrow cells have reported improvements in cardiac function. However, the number of patients enrolled in well-controlled trials is still limited.

As these trials proceed, it seems imperative that we address some of the potential dangers that have frequently been ignored.

One potential danger is that the clinical trials will be performed without appropriate controls or without well-defined end points. The danger seems particularly apparent in trials such as those in acute myocardial infarction in which there is great variability in the size and

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Table 1. Summary of published clinical trials treating myocardial infarction with cellular therapies

Name of study or authors	Cell type	Delivery method	Cell isolation/purification	Diagnosis	No. of patients (exp/control)	Safety and adverse events	Other observations	Length of study
Zohlnhofer et al[14]	G-CSF to mobilize bone marrow	SC	NA	Acute MI	56/58	Safe	No significant effects	4-6 mo
STEMMI; Ripa et al[15]	G-CSF to mobilize bone marrow	SC	NA	Acute ST-elevation MI	36/36	Safe	No significant effects	6 mo
Huttmann et al[16]	G-CSF to mobilize bone marrow	SC	NA	Chronic heart disease	9 ICM/8 ICM controls	ICM may risk increased angina and arrhythmia	4 DCM and 5 ICM NYHA improvement and increased 6-min walking distance	6 mo
Valgimigli et al[17]	G-CSF to mobilize bone marrow	SC	NA	Acute MI	7/7	Safe	LVEF up, EDV down	3, 6 mo and follow-up
REPAIR-AMI; Schachinger et al[18]	BMCs or PBSCs	ICI	Ficoll density gradient sedimentation	Acute MI	103/101	Safe	LVEF up, ESV down, improved contractility at 4 mo; lower mortality, recurrence, and procedures at 1 y	4 mo, 1 y
TOPCARE-AMI; Schachinger et al[19]	BMCs or PBSCs	ICI	Ficoll density gradient sedimentation	Acute MI	30 PBSC and 29 BMC	Safe	LVEF up, ESV down, reduced infarct size	1 y
MAGIC; Kang et al[20]	G-CSF mobilized PBSCs	ICI	COBE Spectra Apheresis System	Reperfused MI	10 PBSC, 10 G-CSF only/7 control	G-CSF alone caused complications	LVEF up, better perfusion and exercise time	6 mo
Archundia et al[21]	G-CSF mobilized PBSCs	IMI in old infarct	Baxter closed circuit apheresis	Old MI	5/10	Safe	Improved contractility	28-52 wk
Yaoita et al[22]	BMCs or G-CSF mobilized PBSCs	IMI	BMCs: Not specified/PBSCs: apheresis	Ischemic heart disease	10	Safe	Increased perfusion	Up to 32 mo
Assmus et al[23]	BMCs or PBSCs	ICI	Ficoll density gradient sedimentation	Healed MI	24 PBSC, 28 BMC/23 control with crossover	Safe	With BMCs or crossover, LVEF up, improved contractility and NYHA; with PBSCs, no significant improvements	3 mo, 3 mo crossover
Lunde et al[24]	BMCs	ICI	Ficoll density gradient sedimentation	Acute MI	47/50	Safe	No significant effects on global left ventricular function	3 wk, 6 mo
BOOST; Meyer et al[25]	BMCs	ICI	Gelatin-polysuccinate density gradient sedimentation	Acute MI	30/30	LVEF normal at 18 mo	LVEF up at 6 months	6-18 mo
Janssens et al[26]	BMCs	ICI	Ficoll density gradient sedimentation	Acute ST-elevation MI	33/34	Safe	Smaller infarcts, improved recovery of systolic functions	4 mo
Fernandez-Aviles et al[27]	BMCs	ICI	Ficoll density gradient sedimentation	Reperfused MI	20/13	Safe	LVEF up, ESV down, wall thickening	6 mo
IACT; Strauer et al[28]	BMCs	ICI	Ficoll density gradient sedimentation	Chronic coronary artery disease	18/18	Safe	LVEF up, O_2 consumption up, viability up, increased WMV, smaller infarct	3 mo

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Table 1. Summary of published clinical trials treating myocardial infarction with cellular therapies (continued)

Name of study or authors	Cell type	Delivery method	Cell isolation/purification	Diagnosis	No. of patients (exp/control)	Safety and adverse events	Other observations	Length of study
Dohmann et al[29]	BMCs	IMI	Ficoll density gradient sedimentation	Ischemic heart failure	14/7	Safe	LVEF up, ESV down, smaller infarct, NYHA score improvement	6 mo
Ruan et al[30]	BMCs	ICI	Not specified	Acute MI	9/11	Safe	LVEF up, EDV up, ESV down	3 mo
Strauer et al[31]	BMCs	ICI	Ficoll density gradient sedimentation	Acute MI	10/10	Safe	LVEF up, WMV up, ESV down increased perfusion	3 mo
Perin et al[32]	BMCs	IMI	Ficoll density gradient sedimentation	Ischemic cardiomyopathy	11/9	Safe	NYHA and CCS angina scores improved, exercise capacity up, perfusion up	6, 12 mo
Hamano et al[33]	BMCs	IMI	COBE Spectra Apheresis System	Ischemic heart disease	5	Safe	Perfusion up in 3/5	1 y
Silva et al[34]	BMCs	IMI	Ficoll density gradient sedimentation	Patients listed for heart transplantation	5	Safe	O_2 consumption up, perfusion up, exercise improved, 4/5 no longer needed heart transplant	6 mo
Tse et al[35]	BMCs	IMI	Ficoll density gradient sedimentation	Ischemic myocardium	8	Safe	Improved perfusion, WMV, and function at infarct	3 mo
Fuchs et al[36]	BMCs	IMI	Ficoll density gradient sedimentation	Advanced coronary artery disease	10	Safe	CCS angina score improved, stress-induced ischemia improved	3 mo
Bartunek et al[37]	$CD133^+$ BMCs	ICI	Ficoll and anti-CD133 MACs	Recent MI	19/16	Various coronary complications	LVEF up, ESP/ESV ratio up, perfusion up, viability up, LVEDV down	4 mo
Stamm et al[38]	$CD133^+$ BMCs	IMI	Ficoll and anti-CD133 MACs	Patients undergoing LAVD	6	Safe	Improved LVEF in 4/6 and perfusion in 5/6	3-9 mo
Chen et al[39]	MSCs	ICI	Percoll density gradient sedimentation	Acute MI	34/35	Safe	LVEF up, LVEDV and ESV down, WMV up, perfusion up, better electromechanics	3 mo
Katritsis et al[40]	MSCs + EPCs	ICI	Ficoll and plastic adherence	Infarcted myocardium	11/11	Safe	Improved contractility, lower wall motion score, increased viability	4 mo
Menasche et al[41]	Skeletal myoblasts	IMI	Biopsy dissociation and plastic culture	Postinfarct left ventricle dysfunction	10	Arrhythmia	LVEF up, scar thickening, NYHA score improvement	10.9 mo
Pagani et al[42]	Skeletal myoblasts	IMI	Biopsy dissociation and plastic culture	Ischemia-damaged myocardium	5	Arrhythmia	More blood vessels	68, 91, 144, and 191 d
Herreros et al[43]	Skeletal myoblasts	IMI	Biopsy dissociation and plastic culture	Nonacute MI	12	Safe	LVEF up, viability up, contractility improved	3 mo

G-CSF indicates granulocyte colony-stimulating factor; SC, subcutaneous; NA, not applicable; MI, myocardial infarcttion; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; NYH, New York Heart Association; LVEF, left ventricular ejection fraction; EDV, end-diastolic volume; BMCs, bone marrow mononuclear cells; PBSCs, peripheral blood stem cells; ICI, intracoronary injection; ESV, end-systolic volume; IMI, intramyocardial injection; WMV, wall movement velocity; CCS, Canadian Cardiovascular Society; MACs, magnetic-assisted cell sorting; LAVD, left ventricular assist device; MSCs, mesenchymal stem cells or multipotent stromal cells; EPCs, endothelial progenitor cells.

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location of the lesions, the outcomes are difficult to predict, and different parameters have been used to assess heart function (Table 1).

Ironically, a second potential risk arises from the striking ability of stem/progenitors cells to enhance repair of tissues and to suppress immune reactions: Several reports demonstrated that MSCs stimulate the growth of cancers in mice.[44,45] The cells apparently enhance growth of the cancer by decreasing immune reactions or by responding to the cancer as "a wound that never heals." Therefore, there is a risk that administering MSCs or similar cells will enhance the growth of a previously undetected cancer in a patient. The risk may be small, but it probably should not be overlooked by the physician, by the patient, or in the consent form. By alerting everyone to the possibility, researchers may be able to avoid repeating the sad episode in the history of viral gene therapy in which a shadow was cast over the whole field by a trial in which 9 of 10 patients with severe combined immunodeficiency disease were cured but 2 patients subsequently developed leukemia because of an unanticipated insertional mutation from a retrovirus.[46]

A related risk that is more difficult to define is that stem/progenitor cells that are extensively expanded in culture may themselves generate tumors in patients. Expansion of cells in culture is an attractive strategy because it makes it possible to administer more stem/progenitor cells than the patient can generate on his or her own. MSCs and related stem/progenitor cells can be expanded in culture as rapidly as or even more rapidly than embryonic stem cells. One important distinction between adult stem/progenitor cells and embryonic stem cells is that the embryonic stem cells are immortal in culture and have a great propensity to generate tumors in mice. In contrast, MSCs senesce after expansion through 40 to 50 population doublings, and early passage cells have not produced tumors. However, researchers have known for a long time that if fibroblasts from mouse embryos are cultured for prolonged periods, they undergo senescence followed by a "crisis" phase in which many of the cells die.[47] The few cells that survive the crisis first become immortal in culture and then, after further expansion, can become tumorogenic. A similar sequence of events was observed with human MSCs that were cultured under stressful conditions for many weeks after which they became immortal, developed unstable chromosomes, and generated tumors in mice.[48] We know of no instance in which culture-expanded cells have generated tumors in patients, but there is clearly some risk in administering stem/progenitor cells that have been extensively expanded in culture. DNA replication is an accurate but imperfect process. Therefore, every cell division has a small chance of introducing deleterious mutations, most of which cannot be detected by karyotyping. The risk of mutations is probably higher with cells that, like embryonic stem cells, are immortal in culture. The risk is probably lower with cells that undergo a limited number of population doublings in culture, retain a normal karyotype, and are not immortal in culture. However, despite our best efforts, stem/progenitor cells are still black boxes. Further research is certainly necessary to understand all their mysterious features and to develop better assays for potentially deleterious changes in culture.

A further danger is posed by cells that are injected in high concentrations into tissues. Concentrated cells injected into tissues can form aggregates, particularly if sheared by passage through small needles under pressure. Also, aggregates of cells with the potential to differentiate can generate their own microenvironment to form nodules of bone or other undesirable structures. Cells such as MSCs rapidly form cell-to-cell adhesions as they are expanded in culture. The adherence junctions must be cut with trypsin or other proteases to lift the cells from culture plates and disperse them. However, the cells in suspension will quickly regenerate the adhesion junctions and aggregate. Therefore, if they are not handled with extreme care, they can produce pulmonary emboli or infarctions after infusion into patients.

Finally, researchers currently face the danger of generating a great deal of confusion by clinical trials in which the cells used are not adequately characterized. The hematopoietic stem cells used in some clinical trials (Table 1) have been well characterized, but the ability of hematopoietic stem cells to repair nonhematopoietic tissues has not been reproducibly demonstrated in animal studies.[49] The use of unfractionated mononucleated cells from bone marrow has little support from animal studies and raises a series of questions about the mechanisms involved. The use of MSCs or related cells also presents problems in that cultures of the cells are heterogeneous, even when generated as single-cell–derived colonies.[1] As a result, there is considerable variability in the properties of different preparations of MSCs used in clinical trials. Unfortunately, there currently are no adequate markers to identify most of the stem/progenitor cells being used. Accordingly, there is a great need to standardize protocols for preparing the cells and to develop more definitive markers.

As research goes forward, there will be a continuing need for careful reanalysis of both the risks and potential benefits to patients. Certainly, researchers will all be sorry if clinical trials with adult stem/progenitor cells do not incorporate some of the simple and essential precautions that can prematurely close down new therapies, in this case, therapies that show great promise of helping millions of patients for whom we can now offer little or no hope.

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Authorship

Contribution: D.J.P. wrote the paper, and S.D.O. prepared the table.

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