Clinical Applications of Blood-Derived and Marrow-Derived Stem Cells for Nonmalignant Diseases

Richard K. Burt; Yvonne Loh; William Pearce; et al.

JAMA. 2008;299(8):925-936 (doi:10.1001/jama.299.8.925)

http://jama.ama-assn.org/cgi/content/full/299/8/925

Clinical Applications of Blood-Derived and Marrow-Derived Stem Cells for Nonmalignant Diseases

Richard K. Burt, MD
Yvonne Loh, MD
William Pearce, MD
Nirat Beohar, MD
Walter G. Barr, MD
Robert Craig, MD
Yanting Wen, MD
Jonathan A. Rapp, MD
John Kessler, MD

Context Stem cell therapy is rapidly developing and has generated excitement and promise as well as confusion and at times contradictory results in the lay and scientific literature. Many types of stem cells show great promise, but clinical application has lagged due to ethical concerns or difficulties in harvesting or safely and efficiently expanding sufficient quantities. In contrast, clinical indications for blood-derived (from peripheral or umbilical cord blood) and bone marrow–derived stem cells, which can be easily and safely harvested, are rapidly increasing.

Objective To summarize new, nonmalignant, nonhematologic clinical indications for use of blood- and bone marrow–derived stem cells.

Evidence Acquisition Search of multiple electronic databases (MEDLINE, EMBASE, Science Citation Index), US Food and Drug Administration [FDA] Drug Site, and National Institutes of Health Web site to identify studies published from January 1997 to December 2007 on use of hematopoietic stem cells (HSCs) in autoimmune, cardiac, or vascular diseases. The search was augmented by hand searching of reference lists in clinical trials, review articles, proceedings booklets, FDA reports, and contact with study authors and device and pharmaceutical companies.

Evidence Synthesis Of 926 reports identified, 323 were examined for feasibility and toxicity, including those with small numbers of patients, interim or substudy reports, and reports on multiple diseases, treatment of relapse, toxicity, mechanism of action, or stem cell mobilization. Another 69 were evaluated for outcomes. For autoimmune diseases, 26 reports representing 854 patients reported treatment-related mortality of less than 1% (2/220 patients) for nonmyeloablative, less than 2% (3/197) for dose-reduced myeloablative, and 13% (13/100) for intense myeloablative regimens, ie, those including total body irradiation or high-dose busulfan. While all trials performed during the inflammatory stage of autoimmune disease suggested that transplantation of HSCs may have a potent disease-remitting effect, remission duration remains unclear, and no randomized trials have been published. For reports involving cardiovascular diseases, including 17 reports involving 1002 patients with acute myocardial infarction, 16 involving 493 patients with chronic coronary artery disease, and 3 meta-analyses, the evidence suggests that stem cell transplantation performed in patients with coronary artery disease may contribute to modest improvement in cardiac function.

Conclusions Stem cells harvested from blood or marrow, whether administered as purified HSCs or mesenchymal stem cells or as an unmanipulated or unpurified product can, under appropriate conditions in select patients, provide disease-ameliorating effects in some autoimmune diseases and cardiovascular disorders. Clinical trials are needed to determine the most appropriate cell type, dose, method, timing of delivery, and adverse effects of adult HSCs for these and other nonmalignant disorders.

JAMA. 2008;299(8):925-936 www.jama.com

Stem cells are undifferentiated cells that through replication have the capability of both self-renewal and differentiation into mature specialized cells. In broad terms, there are 2 types of stem cells, embryonic stem cells and adult stem cells. Human embryonic stem cells are isolated from a 50- to 150-cell, 4- to 5-day-old postfertilization blastocyst. Embryonic stem cells generate every specialized cell in the human body and, while capable of indefinite ex vivo proliferation, exist only transiently in vivo (during embryogenesis). Adult stem cells are located in tissues throughout the body and function as a reservoir to replace damaged or aging cells. Under physiologic conditions, adult stem cells are traditionally thought to be restricted in their differentiation to cell lineages of the organ system in which they are located.

Embryonic stem cells have great promise and versatility but, compared with adult stem cells, are currently difficult to control due to their tendency to form tumors containing all types of tissue, ie, teratomas. Embryonic stem cell biology has been associated with ethical controversy, and feeder cell–free and xenogeneic-free culture methods approved by the US Food and Drug Administration are still being per-

Author Affiliations are listed at the end of this article.
Corresponding Author: Richard K. Burt, MD, Division of Immunotherapy, Department of Medicine, Northwestern University Feinberg School of Medicine, 750 N Lake Shore Dr, Room 649, Chicago, IL 60611 (rburt@northwestern.edu).

fected. In contrast, adult stem cells normally behave well without formation of tumors and follow traditional lineage-specific differentiation patterns, fulfilling their physiologic homologous function of replacing normal turnover, aging, or damaged tissues. For these reasons, this review will be confined to adult stem cells.

Due to the inability to efficiently and safely harvest or expand stem cells from most adult organs (eg, liver, gastrointestinal tract, heart, brain), the majority of human stem cell trials have focused on clinical applications for hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), or both, which can be easily obtained in clinically sufficient numbers from peripheral blood, bone marrow, or umbilical cord blood and placenta.

Bone marrow, peripheral blood stem cells (PBSCs), and umbilical cord blood are all sources of adult HSCs; however, most of the cells in the collected product are mature hematopoietic and immune cells, rather than HSCs. To purify for HSCs, assays for their detection needed to be developed. Hematopoietic stem cell assays may be divided into surface antigen detection by flow cytometry, clonogenic colony-forming assays, and in vivo transplant marrow repopulation assays.[1] The gold standard for HSCs is the ability to repopulate all hematopoietic lineages following marrow-ablative total body irradiation. Serial transplantation of stem cells from the original transplant recipient into secondary and tertiary irradiated recipients reconstitutes hematopoiesis with resultant normal life spans. Serial in vivo transplantation demonstrates the 2 essential functional criteria of HSCs: proliferation to replenish the stem cell compartment (self-renewal) and lifelong production of blood (terminal differentiation).[2,3]

Human hematopoietic progenitor cells are identified by glycoproteins CD34$^+$, CD133$^+$, or both. Most human marrow or blood CD34$^+$ or CD133$^+$ cells are committed progenitors, and only a minority are lifelong repopulating stem cells. A CD34- or CD133-enriched HSC product will reconstitute lifelong hematopoiesis and may be easily purified from the marrow or peripheral blood using commercially available instruments.[4-6]

When cells from a bone marrow aspirate are cultured in plastic flasks, hematopoietic cells and HSCs do not adhere to the plastic and are removed with change of media. The remaining plastic-adherent cells were originally termed colony-forming unit fibroblasts because they formed fibroblast-like colonies ex vivo.[7] Subsequently, these adherent cells have been termed MSCs, an abbreviation for both mesenchymal stromal cells and mesenchymal stem cells. The former refers to the ability of MSCs to contribute to the structural matrix of bone marrow and to support hematopoiesis; the latter describes the ability of MSCs to differentiate under various ex vivo culture conditions into different mesenchymal-derived cells.

MSCs have no unique phenotypic marker. The minimal criteria by the International Society of Cellular Therapy to define MSCs are (1) plastic-adherent in culture; (2) expression of CD105, CD73, and CD90; 3) lack of expression of hematopoietic markers such as CD45, CD34, CD14, CD11b, CD19, CD79a, and HLA-DR; and 4) able to differentiate into osteoblasts, adipocytes, and chondrocytes.[8] The ratio of MSCs to marrow mononuclear cells is estimated to be only 10 MSCs per million marrow cells.[9] Despite relatively low numbers, a 2-mL aspirate of bone marrow can be expanded 500-fold ex vivo to 12 billion to 35 billion MSCs within 3 weeks.[9]

EVIDENCE ACQUISITION

A search of multiple electronic databases (MEDLINE, EMBASE, and Science Citation Index), the Food and Drug Administration Drug Site (http://www.fda.gov), and the National Institutes of Health Web site (http://www.clinicaltrials.gov) was conducted to identify studies published from January 1997 to December 2007 on use of hematopoietic, bone marrow, peripheral blood, mesenchymal, or umbilical cord blood stem cells in autoimmune, cardiac, or vascular disease. This search was augmented by hand searching of reference lists in clinical trials, review articles, proceedings booklets, Food and Drug Administration reports, and contact with study authors and device and pharmaceutical companies. Author names that recurred repeatedly (≥6 times) within a given subject area were also searched for all published reports.

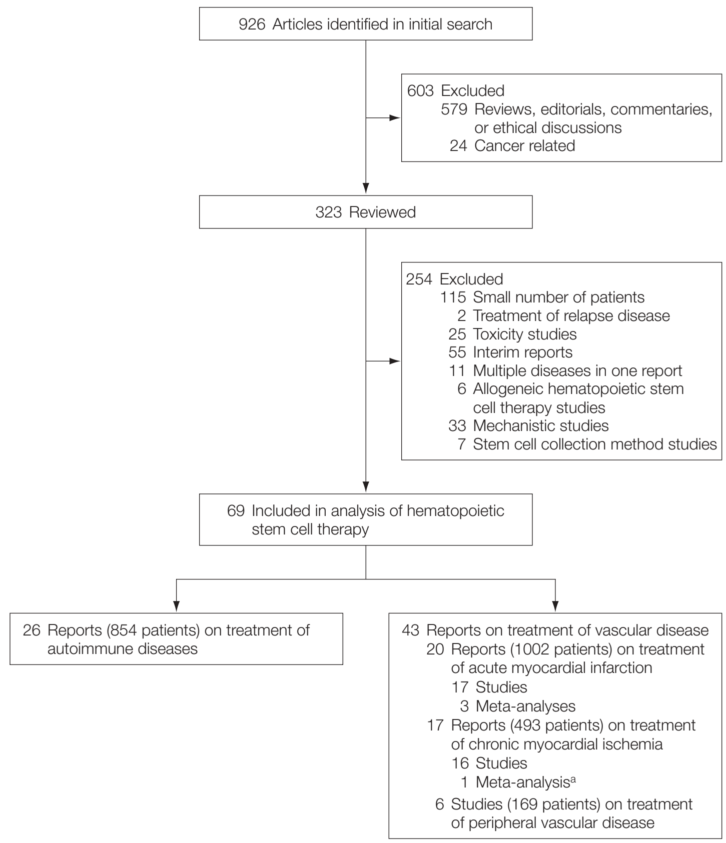
The following data terms were included in the search: *stem cell transplantation, bone marrow transplantation, peripheral blood stem cell transplantation, hematopoietic stem cell transplantation, mesenchymal stem cell transplantation, circulating progenitor cell, autoimmune diseases, multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, Crohn's disease, rheumatoid arthritis, juvenile idiopathic arthritis, vasculitis, Wegner's, Sjögren's, Behcet's, celiac disease, dermatomyositis, polymyositis, relapsing polychondritis, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, diabetes, coronary artery disease, myocardial infarction, myocardial ischemia, coronary circulation, and peripheral vascular disease*. Animal data, abstracts, and non–English-language publications were excluded from the search.

EVIDENCE SYNTHESIS

Four reviewers (R.K.B., Y. W., Y.L., and J.A.R.) judged eligibility of studies independently and simultaneously. The initial search identified 926 articles (FIGURE). Of these, 603 were excluded because they were reviews, editorials, commentaries, ethical discussions, or cancer-related. Another 323 were examined for toxicity and feasibility. These included mechanistic, stem cell collection, or toxicity reports, treatment of relapse, multiple diseases in a single report, interim or substudy reports, and reports with a limited number of patients (≤3 patients with autoimmune disorders, <10 with peripheral vascular disease, <20 with chronic ischemic heart disease, or <30 with acute ischemic heart disease).

Outcome was reviewed in 69 reports (20 on acute ischemic heart disease that included ≥30 patients, 17 on disease [≥20 patients], 6 on peripheral vascular disease [≥10 patients], and 26 on autoimmune disorders [≥4 patients] that reported on a single autoimmune disease and were not subsequently reported as part of a later study or analysis). These 69 reports included 854 patients with autoimmune diseases, 1002 patients with acute myocardial infarction, 493 patients with chronic myocardial ischemia, and 169 with peripheral vascular disease.

Figure. Flow of Eligible Studies of Stem Cell Transplantation for Nonmalignant Nonhematologic Diseases



[a]Assessed both acute infarction and chronic ischemia; this study is also included in the 3 meta-analyses shown above.

Stem Cells for Autoimmune Diseases

Hematopoietic stem cell transplantation (HSCT) for treatment of patients with severe autoimmune diseases began in the late 1990s. These clinical trials were based on extensive preclinical animal transplantation experiments. Some animal autoimmune diseases are environmentally induced by vaccination with self-peptides, adjuvant, or both and may be cured by a syngeneic or pseudoautologous (the animal equivalent of autologous) HSCT. The rationale of autologous HSCT for autoimmune diseases is to immune reset, ie, to generate new self-tolerant lymphocytes after chemotherapy-induced elimination of self- or auto-reactive lymphocytes (ie, lymphoablation). Other animal autoimmune disorders occur spontaneously without intentional or obvious environmental stimuli. These spontaneous-onset animal autoimmune diseases require allogeneic HSCT for cure. Allogeneic HSCT is based on the rationale of both immune reset (similar to autologous HSCT) and of correcting the genetic predisposition to disease by reinfusing non–disease-prone HSCs from a normal donor.

Treatment-related mortality for autologous HSCT of autoimmune diseases in the European Group for Blood and Marrow Transplantation registry is approximately 7%,[10] and some trials have reported rates of up to 23%.[11] Treatment-related mortality, although generally improving with greater experience and more careful patient selection, has justifiably dampened enthusiasm for the field. Autologous HSCT for autoimmune diseases may be performed with either myeloablative or nonmyeloablative regimens.[12] Myeloablative regimens use cancer-specific treatments that destroy the entire marrow compartment, including marrow stem cells, resulting in irreversible and lethal marrow failure if HSCs are not reinfused. Nonmyeloablative regimens are designed specifically for autoimmune diseases, ie, for lymphoablation without irreversible destruction of marrow stem cells. Following a nonmyeloablative regimen, hematopoietic recovery will occur without infusion of HSCs; however, autologous HSCs provide support and shorten the duration of chemotherapy-induced marrow suppression.[13]

The essential argument in favor of nonmyeloablative regimens is that treatment-related mortality needs to be very low for nonmalignant diseases, and nonmyeloablative regimens appear safer than myeloablative regimens[11,14-37] (TABLE 1). A percentage of patients may be cured by autologous HSCT, but—independent of using a myeloablative or nonmyeloablative regimen—disease relapse may occur, and the incidence of serologic remissions and the correlation, if any, to duration of clinical remission has not been evaluated. Therefore, until and unless proven otherwise, autologous HSCT for autoimmune diseases should not be viewed as a cure but rather as changing the natural history of disease. This second point should be considered as the more realistic expectation in justifying mortality end points in favor of nonmyeloablative regimens.

A third point in favor of nonmyeloablative regimens is that immune-mediated diseases may, despite significant morbidity, remit or "burn out." While probability of poor outcomes can be determined for a given population, individual patients who may eventually remit or stabilize spontaneously cannot always be excluded a priori. It is debatable whether a subset of patients who may remit without HSCT should be exposed to myeloablative regimens, especially those including total body irradiation, which cause a relatively high incidence of a more lethal disease, ie, myelodysplastic syndrome (MDS)/leukemia.[12] Treatment of systemic sclerosis and multiple sclerosis with myeloablative regimens including total body irradiation has already been reported to be complicated by

Table 1. Treatment-Related Mortality Following Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases[a]

Source	Disease	Multicenter or Single Center	Treatment-Related Deaths/Patients, No. (%)	Response
Nonmyeloablative Regimen[b]				
Burt et al[c]	Relapsing-remitting MS	Single	0/21 (0)	0% progression at 2 y; 62% improved
Craig et al[d]	Crohn disease	Single	0/21 (0)	100% remission; 33% relapse
Oyama et al,[15] 2007	Systemic sclerosis	Single	0/10 (0)	70% progression-free survival at 2 y
Statkute et al,[16] 2007	Vasculitis	Single	0/4 (0)	Complete remission (n = 3); partial response (n = 1)
Voltarelli et al,[17] 2007	Type 1 diabetes mellitus	Single	0/15 (0)	13/15 patients remaining insulin-free
Vonk et al,[18] 2007	Systemic sclerosis	Multiple	1/26 (4)	64% event-free survival at 5 y[e]
Burt et al,[19] 2006	SLE	Single	1/50 (2)	50% disease-free survival at 5 y
Snowden et al,[21] 2004	Rheumatoid arthritis	Multiple	0/73 (0)[f]	50% ACR criteria 50 or greater response at 12 mo
Total			2/220 (<1)	
Low-Intensity Myeloablative Regimen[g]				
Al-toma et al,[22] 2007	Celiac	Single	0/7 (0)	NA
Ni et al,[23] 2006	Progressive MS[h]	Single	2/21 (9.5)	42% progression-free survival at 42 mo
Xu et al,[24] 2006	Secondary progressive MS	Single	0/22 (0)	77% progression-free survival
Capello et al,[25] 2005	MS	Single	0/21 (0)	20 improved or stable
Carreras et al,[26] 2003	MS	Single	0/14 (0)	3 improved
Fassas et al,[27] 2002	Progressive MS[h]	Single	1/24 (4)	78% improved or stabilized
Kozák et al,[28] 2000	Secondary progressive MS	Single	0/8 (0)	3 improved
Total			3/197 (<2)	
High-Intensity Myeloablative Regimen[i]				
Nash et al,[11] 2007	Systemic sclerosis	Multiple	8/34 (23)[j]	64% progression-free survival at 5 y
Samijin et al,[14] 2006	Secondary progressive MS	Single	1/14 (7)[k]	64% 3-y disease progression
Burt et al,[29] 2003	Secondary progressive MS	Single	1/21 (5)[k]	38% progression in 2 y
Nash et al,[30] 2003	Secondary progressive MS	Multiple	1/26 (4)	27% progression in 3 y
Openshaw et al,[31] 2000	Secondary progressive MS	Single	2/5 (40)	NA
Total			13/100 (13)	
Mixed Myeloablative and Nonmyeloablative Regimens				
Daiker et al,[32] 2007	Vasculitis	Multiple	0/14 (0)	Complete remission (n = 6); partial response (n = 5)
Saccardi et al,[33] 2006	MS[l]	Multiple	10/178 (5.3)[m]	63% improvement or stabilization
De Kleer et al,[34] 2004	JIA	Multiple	3/34 (9)	53% complete remission
Farge et al,[35] 2004	Systemic sclerosis	Multiple	5/57 (8.7)	Complete remission or partial response in 92%
Jayne et al,[36] 2004	SLE	Multiple	7/53 (13)	55% disease-free survival at 5 y
Binks et al,[37] 2001	Systemic sclerosis	Multiple	7/41 (17)	NA
Total			32/337 (9.4)	

Abbreviations: ACR, American College of Rheumatology; CIDP, chronic inflammatory demyelinating polyneuropathy; JIA, juvenile idiopathic arthritis; MS, multiple sclerosis; NA, not available; SLE, systemic lupus erythematosus.

[a] Excludes reports having <4 patients, reports with multiple autoimmune diseases, and results included in interim or substudy analyses.

[b] Nonmyeloablative regimens include combinations of cyclophosphamide, fludarabine, or antilymphocyte antibodies.

[c] R. K. Burt, Y. Loh, B. Cohen, et al., Autologous non-myeloablative hematopoietic stem cell transplantation for relapsing-remitting multiple sclerosis reverses neurologic disability, unpublished data, 2008.

[d] R. M. Craig, Y. Oyama, K. Quigley, et al, Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with refractory Crohn disease 2001-2007, unpublished data, 2008.

[e] Progression-, relapse-, and mortality-free survival.

[f] Two patients received a myeloablative regimen.

[g] Low-intensity myeloablative regimens may include nonmyeloablative agents as well as either BEAM (carmustine, etoposide, cytarabine, melphalan) or melphalan (≤140 mg/m^2).

[h] Not categorized as secondary or primary progressive.

[i] High-intensity myeloablative regimens may include nonmyeloablative agents as well as either total body irradiation (≥8 Gy) or full-dose busulfan.

[j] Does not include 2 cases of late radiation-induced myelodysplastic syndrome/leukemia.

[k] One case of late radiation-induced myelodysplastic syndrome/leukemia included in mortality.

[l] Includes primary and secondary progressive, relapsing progressive, and relapsing-remitting multiple sclerosis.

[m] Transplant-related mortality lower with less intense regimens.

MDS/leukemia,[11,14] an occurrence consistent with the approximately 10% incidence of MDS after autologous HSCT using total body irradiation regimens in low-grade lymphomas.[38,39]

Independent of whether myeloablative or nonmyeloablative regimens are used, another complication, late secondary autoimmune disorders, may arise from some agents used in the conditioning regimen. The initial standard nonmyeloablative regimen of cyclophosphamide and rabbit antithymocyte globulin (rATG) was well tolerated. A second-generation nonmyeloablative regimen used cylophosphamide and a broader- and longer-acting agent, alemtuzumab, instead of rATG. Potential life-threatening secondary autoimmune cytopenias, including idiopathic thrombocytopenic purpura, autoimmune neutropenia, and autoimmune hemolytic anemia, occurred late (2 to 18 months) after transplantation in patients receiving regimens containing alemtuzumab.[40] A third-generation nonmyeloablative regimen, termed "rituximab sandwich," entails 1 dose of rituximab given before and after cyclophosphamide and rATG. To date, this regimen has been well tolerated.

Both early and late toxicity are a consequence of the regimen used for transplantation and of the increase in transplant-related mortality that occurs with increased intensity of the transplant regimen. Treatment-related mortality is less than 1% for nonmyeloablative, less than 2% for low-intensity myeloablative, and 13% for high-intensity myeloablative regimens (Table 1). A number of reports combined data from patients treated with different conditioning regimens or from those with different diseases complicating interpretation, because toxicity is both regimen- and disease-specific (Table 1). Although transplant regimen intensity may correlate with remission duration it is unclear if, at some point in dose intensity, a response plateau occurs independent of any further increase in regimen intensity. It is also unclear if any regimen may be viewed as curative. However, myeloablative as well as nonmyeloablative regimens, regardless of intensity, when used during the inflammatory stage of disease, have demonstrated a potent disease-ameliorating and remission-inducing effect.

In a single experienced center, nonmyeloablative autologous HSCT for patients with systemic lupus erythematosus, when performed as salvage therapy for treatment-refractory disease, resulted in marked serologic, clinical, and organ improvement, with 2% (1/50) treatment-related mortality and 50% probability of maintaining remission for 5 years.[19] In comparison, a multicenter analysis of HSCT for systemic lupus erythematosus that included both myeloablative and nonmyeloablative regimens from 23 different centers reported a similar 55% 5-year disease-free survival, but treatment-related mortality was 13% (7/53).[36]

In patients with systemic sclerosis, autologous HSCT resulted in remarkable reversal of skin tightness, improved joint flexibility and quality of life, and reversal of pulmonary alveolitis.[15,18] Two studies of nonmyeloablative regimens demonstrated 0% (0/10) and 4% (1/26) rates of treatment-related mortality,[15,18] respectively, while a study using a myeloablative approach including total body irradiation reported a rate of 23% (8/34).[11] Both myeloablative[11] and nonmyeloablative[18] approaches reported identical 64% 5-year event-free survival.

For multiple sclerosis, original transplantation regimens were myeloablative and performed predominantly in patients with secondary progressive and, to a lesser extent, primary progressive disease. In this subset of patients, intense myeloablative regimens generally failed to improve neurologic disability or to convincingly halt or change the rate of progressive neurologic disability.[27,29-31] High-intensity myeloablative regimens including total body irradiation or busulfan demonstrated high mortality (including MDS/leukemia),[29-31] whereas BEAM (carmustine, etoposide, cytarabine, melphalan), a less intense myeloablative regimen and the most common regimen used in Europe for multiple sclerosis, was better tolerated with no deaths among the last 53 patients undergoing transplantation.[33] Despite lack of clinical benefit in patients with progressive multiple sclerosis, magnetic resonance imaging evidence of inflammation was abrogated, while loss of brain volume continued for 2 years before subsiding.[41] In retrospect, the predominant pathophysiology in primary and secondary progressive multiple sclerosis is axonal degeneration, which would not be expected to improve after autologous HSCT, a method that allows delivery of intense immune suppression. Learning from these studies, a trial of autologous HSCT for relapsing-remitting multiple sclerosis, which is an immune-mediated inflammatory disease, was performed with a safer nonmyeloablative regimen. There was no treatment-related mortality, no disease progression, and two-thirds of patients had significant improvement in neurologic function (R.K. Burt, Y. Loh, B. Cohen, et al; Autologous non-myeloablative hematopoietic stem cell transplantation for relapsing-remitting multiple sclerosis reverses neurologic disability; unpublished data, 2008).

The lessons learned from multiple sclerosis—ie, treat early while the disease is inflammatory and use nonmyeloablative regimens with low risk of treatment-related mortality—were applied to patients with type 1 diabetes by using a nonmyeloablative regimen and selecting patients within 6 weeks of diagnosis before complete loss of insulin-producing islet cells. Autologous nonmyeloablative HSCT resulted in insulin-free remission of type 1 diabetes in 13 of 15 patients, and some patients have maintained normal blood glucose levels (as determined by levels of glycated hemoglobin) despite no insulin or other therapy for more than 3 years at last follow-up.[17]

Both rheumatoid arthritis and Crohn disease have been treated almost exclusively with nonmyeloablative regimens (Table 1) (R.M. Craig, Y. Oyama, K. Quigley, et al; Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with refractory Crohn disease; unpublished data, 2008).[20,21] For rheumatoid arthritis, the majority achieved at least a 50% or greater response; demonstrated re-

Table 2. Ongoing Randomized Controlled Trials of Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases

Trial	Disease	Country	URL (Trial Identifier)
		Nonmyeloablative Regimen	
ASSIST	Systemic sclerosis	United States/Brazil	http://www.clinicaltrials.gov (NCT00278525)
ASTIL	Systemic lupus erythematosus	Europe	Pending
ASTIS	Systemic sclerosis	Europe	http://www.astistrial.com
KISS	Crohn disease	United States	http://www.clinicaltrials.gov (NCT00271947)
MIST	Multiple sclerosis	United States/ Canada/Brazil	http://www.clinicaltrials.gov (NCT00273364)
		Myeloablative Regimen	
ASTIMS	Multiple sclerosis	Europe	http://www.astims.org
SCOT	Systemic sclerosis	United States	http://www.clinicaltrials.gov (NCT00114530)

Abbreviations: ASSIST, American Scleroderma Stem Cell vs Immune Suppression Trial; ASTIL, Autologous Stem Cell Transplantation International Lupus; ASTIMS, Autologous Stem Cell Transplantation International Multiple Sclerosis; ASTIS, Autologous Stem Cell Transplantation International Scleroderma; KISS, Crohns Immune Suppression vs Stem Cells; MIST, Multiple Sclerosis International Stem Cell Transplant; SCOT, Scleroderma Cyclophosphamide Or Transplantation; URL, uniform resource locator.

newed responsiveness to traditional disease-modifying medications; had reduction in the rate of joint damage for at least 2 years after transplantation[42]; and, when compared with baseline, had improvement on health status assessment questionnaires for at least 5 years.[43] Crohn disease, an immune-mediated disorder that arises from dysregulated immune responses to intestinal pathogens rather than from autoantigens per se, also remitted following autologous nonmyeloablative HSCT (R.M. Craig, Y. Oyama, K. Quigley, et al; Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with refractory Crohn disease; unpublished data, 2008).[20]

Other immune-mediated diseases that have been treated with encouraging initial results by autologous nonmyeloablative or low-intensity myeloablative regimens include chronic inflammatory demyelinating polyneuropathy,[44] relapsing polychondritis,[45] autoimmune-related retinitis and optic neuritis (Y. Oyama, R. K. Burt, C. Thirkill, E. Hanna, K. Merril, J. Keltner; Autoimmune-related retinopathy and optic neuropathy [ARRON] syndrome treated by autologous nonmyeloablative hematopoietic stem cell transplantation; unpublished data, 2008), dermatomyositis/polymyositis,[46] celiac disease,[22] polyarteritis nodosa,[32] neurovascular Behçet disease,[16] neurovascular Sjögren syndrome,[16] Takyasu arteritis,[47] and Wegner granulomatosus.[16] Although results are not yet reported, several randomized controlled trials of autologous HSCT for autoimmune diseases are ongoing, most of which use nonmyeloablative regimens (TABLE 2).

Recently, allogeneic HSCT using a sibling's HSCs has also been reported for treatment of several autoimmune diseases.[48-52] Because it changes genetic predisposition to disease, allogeneic HSCT is considered more likely to cure autoimmune diseases compared with autologous HSCT. Graft-vs-host disease (GVHD), an often more lethal immune-mediated disease, is not an acceptable risk following allogeneic HSCT for autoimmune disorders rather than for malignancies and should be minimized by depletion of lymphocytes from the donor graft. Although yet unproven, some animal and limited human data[48,49,53] suggest that an allogeneic graft-vs-autoimmunity effect may occur without GVHD via use of a lymphocyte-depleted graft.

When administered intravenously without prior chemotherapy or radiotherapy, MSCs have an immune suppressive effect that can ameliorate animal autoimmune diseases, although the mechanisms remain poorly defined.[54] Human trials of MSCs for numerous immune-mediated diseases are being discussed and have been initiated in patients with GVHD. Since MSCs can be easily obtained and culture-expanded, bone marrow– or adipose tissue–derived MSCs from third parties or from the original marrow donor have been infused to modulate refractory GVHD, with reports of beneficial effects in nonrandomized, noncontrolled trials.[55,56] In nonrandomized trials, 94% of patients with acute GVHD responded to intravenous infusion of MSCs.[56]

Stem Cells for Vascular Disease

Numerous animal models of different disease states have reproducibly and repeatedly demonstrated improvement in nonhematopoietic organ function after injection of unmanipulated marrow, peripheral blood, or umbilical cord blood cells, or of enriched HSCs/MSCs. Possible mechanisms by which blood or marrow stem cells improve visceral organ function is cell fusion or transdifferentiation, ie, the phenomenon of in vivo transformation or epigenetic reprogramming of HSCs into somatic cells of nonmarrow, nonhematopoietic lineage such as cardiomyocytes or neurons. While cell fusion and transdifferentiation both may occur ex vivo, the preponderance of evidence suggests that in vivo these mechanisms are not clinically relevant.

The mechanism by which blood- and marrow-derived cells improve nonhematopoietic organ function may be attributable to vasculogenesis from endothelial progenitor cells contained within PBSCs or from bone marrow mononuclear cells (BMMCs) that undergo lineage-specific differentiation into new blood vessels; alternatively, a concept gaining broader acceptance is that numerous stem cells provide a local paracrine or cell-help-cell effect. This chaperone or paracrine effect is mediated through release of growth factors, antiapoptotic proteins, angiogenic proteins, or other trophic factors, immune-modulating factors, and improvement of function through physical remodeling of 3-dimensional architecture. While the exact mechanisms remain controversial, a substantial number of clinical trials have been initiated using BMMCs, PBSCs, purified HSCs, or cultured MSCs to treat vascular diseases.

Acute Myocardial Infarction. In patients with ST-segment elevation myocardial infarction, standard treatment, including percutaneous coronary intervention of the infarct-related artery with or without stent placement plus anticoagulation, has been followed several days to weeks later by repeat percutaneous coronary intervention and intracoronary infusion of stem cells[57-73] (TABLE 3). The infused stem cells have included autologous unmanipulated BMMCs, CD133- or CD34-purified HSCs, unselected PBSCs, MSCs, or circulating progenitor cells (CPCs), which are peripheral blood cells cultured ex vivo to express endothelial characteristics. This mixture of cells, whether unselected, enriched for a stem cell marker, or manipulated in culture and from diverse sources, can be used in intracoronary or intramyocardial transplantation without a clear distinction of superiority of one cellular source or type over another.

The TOPCARE-AMI (Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction) study has published several reports comparing intracoronary transplantation of BMMCs with that of CPCs.[57,74-77] BMMC- as well as CPC-treated patients had similar improvements in infarct size, left ventricular ejection fraction (LVEF), coronary blood flow, and perfusion. Benefit was maintained for at least 12 months.[57]

The REPAIR-AMI (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction) trial compared injection of intracoronary BMMCs with placebo 3 to 7 days after successful percutaneous coronary intervention and demonstrated improved recovery of left ventricular contractility in the cell treatment group.[58] Benefit was also maintained for at least 12 months.[59,78]

The BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial reported that BMMCs significantly improved LVEF 6 months after intracoronary transplantation.[60] In contrast to the TOPCARE-AMI and REPAIR-AMI studies, the BOOST trial reported that the beneficial effect on LVEF was no longer significant after 12 months.[61,62]

Table 3. Clinical Trials of Stem Cell Therapy for Acute Myocardial Infarction With ≥30 Patients

Source	Trial	No. of Patients	Days After Acute MI	Follow-up, mo	Control Infusion	Stem Cell Source	LVEF Outcome, Treatment/Control; Comment
Choi et al,[73] 2007	Unblinded	73	5-19	24	None	Peripheral blood	NS
Kang et al,[64] 2007	MAGIC Cell 1	30	NA[a]	24	G-CSF	Peripheral blood	Improved in infusion group compared to G-CSF
Li et al,[70] 2007	Unblinded	70	6	6	Untreated	Peripheral blood	Improved 7.1%/1.6%
Tatsumi et al,[72] 2007	Unblinded	54	<5	6	None	Peripheral blood	Improved 13.4%/7.4%
Janssens et al,[67] 2006	Randomized	67	1-2	4	Placebo	Bone marrow	3.3%/2.2% reduced infarct size (NS)
Kang et al,[65] 2006	MAGIC Cell-3-DES	82	NA	6	Acute MI/old MI/untreated	Peripheral blood	Improved 5.1%/−0.2%
Lunde et al[63] 2006	ASTAMI	100	4-8	6	None	Bone marrow	Improved 3.1%/2.1% (NS)
Meyer et al,[61] 2006	BOOST	60	4.8[b]	18	None	Bone marrow	Improved 5.9%/3.1% (NS)
Mansour et al,[69] 2006	Nonrandomized	38	NA	4-8	None	CD133	LVEF not examined; increased infarct-related artery restenosis
Meluzin et al,[71] 2006	Randomized[c]	66	5-9	3	None	Bone marrow	Improved 5%/2% in high dose
Schächinger et al,[58] 2006	REPAIR-AMI	204	3-7	4	Placebo	Bone marrow	Improved 5.5%/3.0%
Schächinger et al,[59] 2006	REPAIR-AMI	204	3-7	12	Placebo	Bone marrow	Improved outcome of death, reinfarction, revascularization
Schaefer et al,[62] 2006	BOOST	59	4.5[b]	18	None	Bone marrow	Improved diastolic function (NS)
Bartunek et al,[68] 2005	Unblinded	35	11.6[c]	4	None	CD133	Improved/increased infarct-related artery restenosis
Chen et al,[66] 2004	Randomized	69	>18	6	Placebo	Mesenchymal	Improved 18%/6%
Schächinger et al,[57] 2004	TOPCARE-AMI	54	3-7	12	None	Bone marrow or CPCs	Improved 8% for both bone marrow and CPCs at 4 mo
Wollert et al,[60] 2004	BOOST	60	4.8[b]	6	None	Bone marrow	Improved 6.7%/0.7%

Abbreviations: ASTAMI, Autologous Stem Cell Transplantation in Acute Myocardial Infarction; BOOST, Bone Marrow Transfer to Enhance ST Elevation Infarct Regeneration Trial; CPC, circulating progenitor cell; G-CSF, granulocyte colony–stimulating factor; LVEF, left ventricular ejection fraction; MAGIC, Myocardial Regeneration and Angiogenesis in Myocardial Infarction With G-CSF and Intracoronary Stem Cell Infusion; MAGIC Cell-3-DES, MAGIC-3-Drug Eluting Stents; MI, myocardial infarction; NA, not available; NS, not significant; REPAIR-AMI, Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction; TOPCARE-AMI, Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction.
[a] Study assessed both acute and old MI.
[b] Mean value.
[c] Randomized to high-dose, low-dose, or no cells.

The ASTAMI (Autologous Stem Cell Transplantation in Acute Myocardial Infarction) trial found no significant beneficial effects from intracoronary transplantation of BMMCs on LVEF.[63] Compared with controls, BMMCs tended to improve LVEF as demonstrated by echocardiography (3.1%-2.1%) and single photon emission computed tomography (8.1%-7.0%) and tended to diminish infarct size (−11% to −7.8%). These changes were not significantly different.

The MAGIC (Myocardial Regeneration and Angiogenesis in Myocardial Infarction With G-CSF and Intracoronary Stem Cell Infusion) Cell 1 study compared intracoronary transplant of granulocyte colony–stimulating factor (G-CSF)–mobilized PBSCs vs treatment with G-CSF alone vs an untreated control group.[64,79] Left ventricular ejection fraction improved in the PBSC group compared with the G-CSF-alone group, and there was an increase in restenosis in patients receiving G-CSF. The subsequent MAGIC Cell-3-DES (Myocardial Regeneration and Angiogenesis in Myocardial Infarction With G-CSF and Intracoronary Stem Cell Infusion-3-Drug Eluting Stents) study compared intracoronary transplantation of G-CSF–mobilized PBSCs vs an untreated control group.[65] Left ventricular ejection fraction and remodeling improved compared with controls in the cell-treated group with acute myocardial infarction. Significant improvement in LVEF has been reported following injection of MSCs as well as of BMMCs, CPCs, and PBSCs.[66]

Taken as a whole, the results of intracoronary transplantation of progenitor cells following ST-segment elevation acute myocardial infarction are generally viewed as conveying a modest benefit. Single-group studies must be tempered by the realization that LVEF normally improves a few months after acute myocardial infarction, even without stem cell transplantation. Interstudy and intrastudy reproducibility of LVEF demonstrated by echocardiography and cardiovascular magnetic resonance imaging varies significantly, with conservative estimates of 8.6% and 2.4%, respectively.[80] Reproducibility of LVEF measurement, therefore, overlaps with anticipated improvement (2%-5%) from stem cell transplantation. Nevertheless, 3 separate meta-analyses of controlled clinical trials of stem cell therapy in acute myocardial infarction have indicated modest benefit.[81-83]

Chronic Coronary Artery Disease. In chronic ischemic cardiac disease or old myocardial infarction, noncontracting but viable myocardium, termed hibernating myocardium, is a physiologic response to hypoxic stress that halts the energy demands of contraction to prevent cardiomyocyte death. In the laboratory, hibernating myocardium is identified by areas of electromechanical dissociation, ie, myocardium that conducts electricity but does not contract.

Initial trials using stem cells in old myocardial infarction or chronic ischemia involved thoracotomy and coronary artery bypass graft surgery with simultaneous epicardial-directed intramyocardial injection of BMMCs or PBSCs while the heart was still arrested during cardiopulmonary bypass. Subsequently, most patients with chronic ischemic heart disease received stem cells by either percutaneous intracoronary or endomyocardial delivery without undergoing simultaneous coronary artery bypass graft surgery[84-99] (TABLE 4). Erbs et al[84] treated chronic (>30-day) total coronary occlusion with recanalization, followed 10 days later by randomization to intracoronary CPC infusion or no cells. Patients receiving CPCs had significant improvement in LVEF. In the IACT (Intracoronary Autologous Bone Marrow Cell Transplantation in Chronic Coronary Artery Disease) trial, Strauer et al[85] treated old myocardial infarction (5 months to 8.5 years prior) with intracoronary BMMCs, with significant improvement in LVEF. Assmus et al[86] randomized 75 patients in the TOPCARE-CHD (Transplantation of Progenitor Cells and Recovery of Left Ventricular Function in Patients With Chronic Ischemic Heart Disease) trial to intracoronary infusion of BMMCs, CPCs, or no cells. Bone marrow mononuclear cells, but not CPCs, improved LVEF compared with controls[86]; if heart failure was present, injection of BMMCs resulted in significant reduction of brain natriuretic peptide, a serum marker for heart failure.[87]

In summary, pump failure has been a historically vexing problem and, despite maximizing medical therapy, often progressive and irreversible. Symptomatic relief of pain may be a placebo effect. Nevertheless, stem cell treatment of chronic myocardial ischemia has generally been reported to increase regional perfusion, wall motion, and global LVEF, and to relieve angina pectoris. A recent meta-analysis reported a modest association between blood- or marrow-derived stem cell injection and improvement in chronic ischemic heart disease.[81]

Peripheral Vascular Disease. Tissue limb ischemia from peripheral vascular disease usually manifests in the lower extremities and may be due to thromboangiitis obliterans (Buerger disease) or atherosclerosis obliterans. The mainstay of treatment for peripheral vascular disease has been surgical revascularization. Patients with critical limb ischemia that have exhausted operative revascularization procedures are traditionally treated by limb amputation. Several reports have suggested that injection of blood- or bone marrow–derived stem cells into the affected limb may have some benefit. As in cardiac disease, a variety of stem cell sources have been used, including unselected bone marrow, G-CSF–mobilized PBSCs, MSCs, CPCs, and purified CD34 or CD133 stem cells obtained from marrow or peripheral blood.

Progenitor cells are injected directly via a syringe through a 22- to 26-gauge needle into multiple sites 1 to 3 cm apart into the gastrocnemius/soleus muscle or into the foot or quadriceps muscle, or both, of the involved leg. The procedure has generally been performed safely, although 1 case of an arteriovenous fistula at the injection site has been reported.[100] While most investigators prefer percutaneous injection into the muscle, equally encouraging results are obtained by intra-arterial injection of cells into the involved extremity or by fenestration (ie, puncturing the tibia) to allow bone marrow cells to leak into adjacent muscle.[101-103]

Most patients experience relief of symptomatic pain, limb salvage, and functional improvement. In some cases, ischemic ulcer healing and the ankle-brachial index (a measure of ankle blood flow) improves. In 2 studies, all patients with thromboangiitis obliterans responded to therapy.[103,104] In contrast, depending on the report, approximately two-thirds (70%) of patients with atherosclerosis obliterans responded.[105]

The TACT (Therapeutic Angiogenesis by Cell Transplantation) trial enrolled patients with bilateral (n=22) or unilateral (n=25) peripheral vascular disease.[106] Investigators injected one leg with BMMCs and the other with blood. The pain-free walking time, ankle-brachial index, and transcutaneous oxygen pressure improved significantly in the BMMC-injected legs compared with those injected with blood. A second randomized trial, TAM-PAD (Transplant of Autologous Mononuclear Bone Marrow Cells in Peripheral Arterial Disease), combined intra-arterial and intramuscular injection of BMMCs.[102] The group receiving BMMCs (n=13) had significantly improved pain-free walking time, ankle-brachial index, and capillary-venous oxygen saturation.[102]

Duration of improvement following injection of progenitor cells remains unclear but may persist beyond 1 year. The dose of injected CD34$^+$ cells may affect efficacy.[107] Injected BMMCs are thought to secrete numerous cytokines, such as vascular endothelial growth factor, that may induce local angiogenesis, recruit circulating CD34$^+$ cells for vasculogenesis, or release factors such as nitric oxide that augment local endothelial cell attempts at vasodilation.[108]

COMMENT

The use of adult HSCs is rapidly expanding beyond the traditional applications for malignancy. In autoimmune diseases, chemotherapy to ablate the disease-causing immune system is followed by infusion of unmanipulated autologous bone marrow, PBSCs, or purified CD34$^+$ HSCs to reconstitute immunopoiesis or hematopoiesis.

Autologous HSCT, while probably not a "cure," appears to be a potentially useful clinical approach available to ameliorate autoimmune disease activity. However, HSCT has been complicated by significant treatment-related mortality and late MDS/leukemia when intense myeloablative regimens are used, indicating the need for development of safer nonmyeloablative regimens and restriction of this technique to experienced centers. Allogeneic (sibling or umbilical cord blood) transplantation of HSCs ultimately may prove to be the elusive "cure" for some autoimmune disorders, but allogeneic HSCT must be performed without risk of GVHD by lymphocyte depletion of the donor graft, and whether an allogeneic graft-vs-autoimmunity effect can occur without GVHD remains unproven.

Unmanipulated bone marrow, peripheral blood stem cells, and purified HSCs and MSCs infused without prior chemotherapy have been used to facilitate tissue repair following ischemic injury. Randomized trials have suggested modest benefit with little toxicity from stem

Table 4. Clinical Trials of Stem Cell Therapy for Chronic Myocardial Ischemia and/or Heart Failure With ≥20 Patients

Source	Trial Type/Name	No. of Patients	Follow-up, mo	Stem Cell Route	Stem Cell Source	LVEF Outcome; Comment
Assmus et al,[87] 2007	TOPCARE-CHD	121	19	Intracoronary	Bone marrow	Improved mortality in high-order CFUs injected
Losordo et al,[97] 2007	Randomized	24	12	Intramyocardial	CD34	Not examined
Manginas et al,[96] 2007	Unblinded	24	28	Intracoronary	CD133, CD34	Improved LVEF and left ventricular volumes
Stamm et al,[99] 2007	Unblinded	40	6	Intramyocardial	CD133	Improved LVEF
Assmus et al,[86] 2006	TOPCARE-CHD Randomized	75	3	Intracoronary	Bone marrow/ CPCs	Improved with bone marrow
Beeres et al,[93] 2006	Single group	25	12	Intramyocardial	Bone marrow	Improved LVEF, CCS angina score, perfusion
Chen et al,[95] 2006	Unblinded	45	12	Intracoronary	Mesenchymal	Improved ischemia, NYHA class, and LVEF
Fuchs et al,[92] 2006	Single group	27	12	Intramyocardial	CD34	Improved CCS angina score
Gao et al,[94] 2006	Unblinded	28	3	Intracoronary	Bone marrow	Improved LVEF, improvement in CHF
Hendrikx et al,[91] 2006	Randomized	20	4	Intramyocardial	Bone marrow	NS
Mocini et al,[98] 2006	CABG + cells or CABG alone	36	12	Intramyocardial	Bone marrow	Improved LVEF and wall motion
Erbs et al,[84] 2005	Randomized	26	3	Intracoronary	CPCs	Improved
Patel et al,[90] 2005	Randomized	20	6	Intramyocardial	CD34	Improved
Strauer et al,[85] 2005	IACT[a]	36	3	Intracoronary	Bone marrow	Improved
Perin et al,[88] 2004	Sequential enrollment; treatment or control	20	12	Intramyocardial	Bone marrow	NS
Perin et al,[89] 2003	Single group	21	4	Intramyocardial	Bone marrow	Improved

Abbreviations: CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; CFU, colony-forming unit; CHF, congestive heart failure; CPC, circulating progenitor cell; IACT, Intracoronary Autologous Bone Marrow Cell Transplantation in Chronic Coronary Artery Disease; LVEF, left ventricular ejection fraction; NS, not significant; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; TOPCARE-CHD, Transplantation of Progenitor Cells and Recovery of Left Ventricular Function in Patients With Chronic Ischemic Heart Disease.
[a]Control group refused treatment with bone marrow-derived cells.

cell therapy in cardiac disease and peripheral vascular disease. The mechanisms of this effect remain undefined and have evolved from cell fusion and transdifferentiation to endothelial progenitor cell–derived vasculogenesis and local paracrine effects. Clinical trials are needed to determine the most appropriate cell type, dose, method, and timing of delivery for use of HSCs in cardiovascular disease. Similar trials are also being considered or have recently been initiated in liver disease,[109-111] cerebrovascular disease, and spinal cord injury.

Author Affiliations: Divisions of Immunotherapy (Drs Burt, Craig, and Wen), Cardiology (Drs Beohar and Rapp), Rheumatology (Dr Barr), and Gastroenterology (Dr Craig), Department of Medicine; Division of Vascular Surgery, Department of Surgery (Dr Pearce); and Department of Neurology (Dr Kessler), Northwestern University Feinberg School of Medicine, Chicago, Illinois; and Department of Hematology, Singapore General Hospital, Singapore (Dr Loh).

Author Contributions: Dr Burt had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Burt, Beohar.
Acquisition of data: Burt, Loh, Barr, Wen, Rapp.
Analysis and interpretation of data: Burt, Pearce, Beohar, Craig, Rapp, Kessler.
Drafting of the manuscript: Burt, Beohar.
Critical revision of the manuscript for important intellectual content: Burt, Loh, Pearce, Beohar, Barr, Craig, Wen, Rapp, Kessler.
Administrative, technical, or material support: Burt, Loh, Beohar, Barr, Wen.
Financial Disclosures: None reported.
Additional Contributions: We thank Donald Orlic, PhD (National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland), and Douglas Losordo, MD (Feinberg Cardiovascular Research Institute, Northwestern University, Chicago, Illinois), for critical review of the manuscript. Neither of these individuals received extra compensation for their contributions.

REFERENCES

1. van Os R, Kamminga LM, de Haan G. Stem cell assays: something old, something new, something borrowed. *Stem Cells*. 2004;22(7):1181-1190.
2. Jordan CT, Lemischka IR. Clonal and systemic analysis of long-term hematopoiesis in the mouse. *Genes Dev*. 1990;4(2):220-232.
3. Morrison SJ, Uchida N, Weissman IL. The biology of hematopoietic stem cells. *Annu Rev Cell Dev Biol*. 1995;11:35-71.
4. Berenson RJ, Andrews RG, Bensinger WI, et al. Antigen CD34+ marrow cells engraft lethally irradiated baboons. *J Clin Invest*. 1988;81(3):951-955.
5. Civin CI, Trischmann T, Kadan NS, et al. Highly purified CD34-positive cells reconstitute hematopoiesis. *J Clin Oncol*. 1996;14(8):2224-2233.
6. Gallacher L, Murdoch B, Wu DM, Karanu FN, Keeney M, Bhatia M. Isolation and characterization of human CD34(-)Lin(-) and CD34(+)Lin(-) hematopoietic stem cells using cell surface markers AC133 and CD7. *Blood*. 2000;95(9):2813-2820.
7. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet*. 1970;3(4):393-403.
8. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells: the International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8(4):315-317.
9. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284(5411):143-147.
10. Gratwohl A, Passweg J, Bocelli-Tyndall C, et al; Autoimmune Diseases Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Autologous hematopoietic stem cell transplantation for autoimmune diseases. *Bone Marrow Transplant*. 2005;35(9):869-879.
11. Nash RA, McSweeney PA, Crofford LJ, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. *Blood*. 2007;110(4):1388-1396.
12. Burt RK, Marmont A, Oyama Y, et al. Randomized controlled trials of autologous hematopoietic stem cell transplantation for autoimmune diseases: the evolution from myeloablative to lymphoablative transplant regimens. *Arthritis Rheum*. 2006;54(12):3750-3760.
13. Statkute L, Verda L, Oyama Y, et al. Mobilization, harvesting and selection of peripheral blood stem cells in patients with autoimmune diseases undergoing autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2007;39(6):317-329.
14. Samijn JP, te Boekhorst PA, Mondria T, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2006;77(1):46-50.
15. Oyama Y, Barr WG, Statkute L, et al. Autologous non-myeloablative hematopoietic stem cell transplantation in patients with systemic sclerosis. *Bone Marrow Transplant*. 2007;40(6):549-555.
16. Statkute L, Oyama Y, Barr WG, et al. Autologous non-myeloablative hematopoietic stem cell transplantation for refractory systemic vasculitis [published online ahead of print October 18, 2007]. *Ann Rheum Dis*. doi:10.1136/ard.2007.070227.
17. Voltarelli JC, Couri CE, Stracieri AB, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA*. 2007;297(14):1568-1576.
18. Vonk MC, Marjanovic Z, van den Hoogen FH, et al. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis [published online ahead of print May 25, 2007]. *Ann Rheum Dis*. 2008;67(1):98-104. doi:10.1136/ard.2007.071464.
19. Burt RK, Traynor A, Statkute L, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA*. 2006;295(5):527-535.
20. Oyama Y, Craig RM, Traynor AE, et al. Autologous hematopoietic stem cell transplantation in patients with refractory Crohn's disease. *Gastroenterology*. 2005;128(3):552-563.
21. Snowden JA, Passweg J, Moore JJ, et al. Autologous hemopoietic stem cell transplantation in severe rheumatoid arthritis: a report from the EBMT and ABMTR. *J Rheumatol*. 2004;31(3):482-488.
22. Al-toma A, Visser OJ, van Roessel HM, et al. Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. *Blood*. 2007;109(5):2243-2249.
23. Ni XS, Ouyang J, Zhu WH, Wang C, Chen B. Autologous hematopoietic stem cell transplantation for progressive multiple sclerosis: report of efficacy and safety at three yr of follow up in 21 patients. *Clin Transplant*. 2006;20(4):485-489.
24. Xu J, Ji BX, Su L, Dong HQ, Sun XJ, Liu CY. Clinical outcomes after autologous haematopoietic stem cell transplantation in patients with progressive multiple sclerosis. *Chin Med J (Engl)*. 2006;119(22):1851-1855.
25. Capello E, Saccardi R, Murialdo A, et al; Italian GITMO-Neuro Intergroup on ASCT for Multiple Sclerosis. Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis. *Neurol Sci*. 2005;26(suppl 4):S200-S203.
26. Carreras E, Saiz A, Marín P, et al. CD34+ selected autologous peripheral blood stem cell transplantation for multiple sclerosis: report of toxicity and treatment results at one year of follow-up in 15 patients. *Haematologica*. 2003;88(3):306-314.
27. Fassas A, Passweg JR, Anagnostopoulos A, et al; Autoimmune Disease Working Party of the EBMT (European Group for Blood and Marrow Transplantation). Hematopoietic stem cell transplantation for multiple sclerosis: a retrospective multicenter study [published correction appears in *J Neurol*. 2002;249(11)1619]. *J Neurol*. 2002;249(8):1088-1097.
28. Kozák T, Havrdová E, Pit'ha J, et al. High-dose immunosuppressive therapy with PBPC support in the treatment of poor risk multiple sclerosis. *Bone Marrow Transplant*. 2000;25(5):525-531.
29. Burt RK, Cohen BA, Russell E, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. *Blood*. 2003;102(7):2373-2378.
30. Nash RA, Bowen JD, McSweeney PA, et al. High-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation for severe multiple sclerosis. *Blood*. 2003;102(7):2364-2372.
31. Openshaw H, Lund BT, Kashyap A, et al. Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: report of toxicity and immunological monitoring. *Biol Blood Marrow Transplant*. 2000;6(5A):563-575.
32. Daikeler T, Kötter I, Bocelli Tyndall C, et al; EBMT Autoimmune Diseases Working Party. Haematopoietic stem cell transplantation for vasculitis including Behcet's disease and polychondritis: a retrospective analysis of patients recorded in the European Bone Marrow Transplantation and European League Against Rheumatism databases and a review of the literature. *Ann Rheum Dis*. 2007;66(2):202-207.
33. Saccardi R, Kozak T, Bocelli-Tyndall C, et al; Autoimmune Diseases Working Party of EBMT. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. *Mult Scler*. 2006;12(6):814-823.
34. De Kleer IM, Brinkman DM, Ferster A, et al. Autologous stem cell transplantation for refractory juvenile idiopathic arthritis: analysis of clinical effects, mortality, and transplant related morbidity. *Ann Rheum Dis*. 2004;63(10):1318-1326.
35. Farge D, Passweg J, van Laar JM, et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR registry. *Ann Rheum Dis*. 2004;63(8):974-981.
36. Jayne D, Passweg J, Marmont A, et al; European Group for Blood and Marrow Transplantation, European League Against Rheumatism Registry. Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus*. 2004;13(3):168-176.
37. Binks M, Passweg JR, Furst D, et al. Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. *Ann Rheum Dis*. 2001;60(6):577-584.
38. Montoto S, Canals C, Rohatiner AZ, et al; EBMT Lymphoma Working Party. Long-term follow-up of high-dose treatment with autologous haematopoietic progenitor cell support in 693 patients with follicular lymphoma: an EBMT registry study [published online ahead of print July 19, 2007]. *Leukemia*. 2007;21(11):2324-2331. doi:10.1038/sj.leu.2404850.

39. Brown JR, Feng Y, Gribben JG, et al. Long-term survival after autologous bone marrow transplantation for follicular lymphoma in first remission. *Biol Blood Marrow Transplant*. 2007;13(9):1057-1065.
40. Loh Y, Oyama Y, Statkute L, et al. Development of a secondary autoimmune disorder after hematopoietic stem cell transplantation for autoimmune diseases: role of conditioning regimen used. *Blood*. 2007;109(6):2643-2648.
41. Rocca MA, Mondria T, Valsasina P, et al. A three-year study of brain atrophy after autologous hematopoietic stem cell transplantation in rapidly evolving secondary progressive multiple sclerosis. *AJNR Am J Neuroradiol*. 2007;28(9):1659-1661.
42. Verburg RJ, Flierman R, Sont JK, et al. Outcome of intensive immunosuppression and autologous stem cell transplantation in patients with severe rheumatoid arthritis is associated with the composition of synovial T cell infiltration. *Ann Rheum Dis*. 2005;64(10):1397-1405.
43. Teng YK, Verburg RJ, Sont JK, van den Hout WB, Breedveld FC, van Laar JM. Long-term followup of health status in patients with severe rheumatoid arthritis after high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. *Arthritis Rheum*. 2005;52(8):2272-2276.
44. Oyama Y, Sufit R, Loh Y, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation for refractory CIDP. *Neurology*. 2007;69(18):1802-1803.
45. Rosen O, Thiel A, Massenkeil G, et al. Autologous stem-cell transplantation in refractory autoimmune diseases after in vivo immunoablation and ex vivo depletion of mononuclear cells. *Arthritis Res*. 2000;2(4):327-336.
46. Oryoji K, Himeji D, Nagafuji K, et al. Successful treatment of rapidly progressive interstitial pneumonia with autologous peripheral blood stem cell transplantation in a patient with dermatomyositis. *Clin Rheumatol*. 2005;24(6):637-640.
47. Voltarelli JC, Oliveira MC, Stracieri AB, et al. Haematopoietic stem cell transplantation for refractory Takayasu's arteritis. *Rheumatology (Oxford)*. 2004;43(10):1308-1309.
48. Burt RK, Oyama Y, Verda L, et al. Induction of remission of severe and refractory rheumatoid arthritis by allogeneic mixed chimerism. *Arthritis Rheum*. 2004;50(8):2466-2470.
49. Loh Y, Oyama Y, Statkute L, et al. Nonmyeloablative allogeneic hematopoietic stem cell transplantation for severe systemic sclerosis: graft-versus-autoimmunity without graft-versus-host disease? [published online ahead of print February 19, 2007]. *Bone Marrow Transplant*. 2007;39(7):435-437. doi:10.1038/sj.bmt.1705611.
50. Nash RA, McSweeney PA, Nelson JL, et al. Allogeneic marrow transplantation in patients with severe systemic sclerosis: resolution of dermal fibrosis. *Arthritis Rheum*. 2006;54(6):1982-1986.
51. Marmont AM, Gualandi F, Piaggio G, et al. Allogeneic bone marrow transplantation (BMT) for refractory Behcet's disease with severe CNS involvement. *Bone Marrow Transplant*. 2006;37(11):1061-1063.
52. Marmont AM, Gualandi F, Van Lint MT, Bacigalupo A. Refractory Evans' syndrome treated with allogeneic SCT followed by DLI: demonstration of a graft-versus-autoimmunity effect. *Bone Marrow Transplant*. 2003;31(5):399-402.
53. Verda L, An Kim D, Ikehara S, et al. Hematopoietic mixed chimerism derived from allogeneic embryonic stem cells prevents autoimmune diabetes mellitus in nod mice [published online ahead of print November 1, 2007]. *Stem Cells*. 2007;0:2006-0262v1.
54. Uccelli A, Pistoia V, Moretta L. Mesenchymal stem cells: a new strategy for immunosuppression? *Trends Immunol*. 2007;28(5):219-226.
55. Ringdén O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation*. 2006;81(10):1390-1397.
56. Fang B, Song YP, Liao LM, Han Q, Zhao RC. Treatment of severe therapy-resistant acute graft-versus-host disease with human adipose tissue-derived mesenchymal stem cells. *Bone Marrow Transplant*. 2006;38(5):389-390.
57. Schächinger V, Assmus B, Britten MB, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. *J Am Coll Cardiol*. 2004;44(8):1690-1699.
58. Schächinger V, Erbs S, Elsasser A, et al. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med*. 2006;355(12):1210-1221.
59. Schächinger V, Erbs S, Elsässer A, et al; REPAIR-AMI Investigators. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J*. 2006;27(3):2775-2783.
60. Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet*. 2004;364(9429):141-148.
61. Meyer GP, Wollert KC, Lotz J, et al. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. *Circulation*. 2006;113(10):1287-1294.
62. Schaefer A, Meyer GP, Fuchs M, et al. Impact of intracoronary bone marrow cell transfer on diastolic function in patients after acute myocardial infarction: results from the BOOST trial. *Eur Heart J*. 2006;27(8):929-935.
63. Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med*. 2006;355(12):1199-1209.
64. Kang HJ, Kim HS, Koo BK, et al. Intracoronary infusion of the mobilized peripheral blood stem cell by G-CSF is better than mobilization alone by G-CSF for improvement of cardiac function and remodeling: 2-year follow-up results of the Myocardial Regeneration and Angiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion (MAGIC Cell) 1 trial. *Am Heart J*. 2007;153(2):237.e1-8.
65. Kang HJ, Lee HY, Na SH, et al. Differential effect of intracoronary infusion of mobilized peripheral blood stem cells by granulocyte colony-stimulating factor on left ventricular function and remodeling in patients with acute myocardial infarction versus old myocardial infarction: the MAGIC Cell-3-DES randomized, controlled trial. *Circulation*. 2006;114(1)(suppl):I145-I151.
66. Chen SL, Fang WW, Ye F, et al. Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *Am J Cardiol*. 2004;94(1):92-95.
67. Janssens S, Dubois C, Bogaert J, et al. Autologous bone marrow-derived stem-cell transfer in patients with ST-segment elevation myocardial infarction: double-blind, randomised controlled trial. *Lancet*. 2006;367(9505):113-121.
68. Bartunek J, Vanderheyden M, Vandekerckhove B, et al. Intracoronary injection of CD133-positive enriched bone marrow progenitor cells promotes cardiac recovery after recent myocardial infarction: feasibility and safety. *Circulation*. 2005;112(9)(suppl):I178-I183.
69. Mansour S, Vanderheyden M, De Bruyne B, et al. Intracoronary delivery of hematopoietic bone marrow stem cells and luminal loss of the infarct-related artery in patients with recent myocardial infarction. *J Am Coll Cardiol*. 2006;47(8):1727-1730.
70. Li ZQ, Zhang M, Jing YZ, et al. The clinical study of autologous peripheral blood stem cell transplantation by intracoronary infusion in patients with acute myocardial infarction (AMI). *Int J Cardiol*. 2007;115(1):52-56.
71. Meluzin J, Mayer J, Groch L, et al. Autologous transplantation of mononuclear bone marrow cells in patients with acute myocardial infarction: the effect of the dose of transplanted cells on myocardial function. *Am Heart J*. 2006;152(5):975.e9-15.
72. Tatsumi T, Ashihara E, Yasui T, et al. Intracoronary transplantation of non-expanded peripheral blood-derived mononuclear cells promotes improvement of cardiac function in patients with acute myocardial infarction. *Circ J*. 2007;71(8):1199-1207.
73. Choi JH, Choi J, Lee WS, et al. Lack of additional benefit of intracoronary transplantation of autologous peripheral blood stem cell in patients with acute myocardial infarction. *Circ J*. 2007;71(4):486-494.
74. Assmus B, Schachinger V, Teupe C, et al. Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation*. 2002;106(24):3009-3017.
75. Britten MB, Abolmaali ND, Assmus B, et al. Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. *Circulation*. 2003;108(18):2212-2218.
76. Döbert N, Britten M, Assmus B, et al. Transplantation of progenitor cells after reperfused acute myocardial infarction: evaluation of perfusion and myocardial viability with FDG-PET and thallium SPECT. *Eur J Nucl Med Mol Imaging*. 2004;31(8):1146-1151.
77. Schächinger V, Assmus B, Honold J, et al. Normalization of coronary blood flow in the infarct-related artery after intracoronary progenitor cell therapy: intracoronary Doppler substudy of the TOPCARE-AMI trial. *Clin Res Cardiol*. 2006;95(1):13-22.
78. Erbs S, Linke A, Schächinger V, et al. Restoration of microvascular function in the infarct-related artery by intracoronary transplantation of bone marrow progenitor cells in patients with acute myocardial infarction: the Doppler substudy of the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI) trial. *Circulation*. 2007;116(4):366-374.
79. Kang HJ, Kim HS, Zhang SY, et al. Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. *Lancet*. 2004;363(9411):751-756.
80. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am J Cardiol*. 2002;90(1):29-34.
81. Abdel-Latif A, Bolli R, Tleyjeh IM, et al. Adult bone marrow-derived cells for cardiac repair: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167(10):989-997.
82. Lipinski MJ, Biondi-Zoccai GG, Abbate A, et al. Impact of intracoronary cell therapy on left ventricular function in the setting of acute myocardial infarction: a collaborative systematic review and meta-analysis of controlled clinical trials. *J Am Coll Cardiol*. 2007;50(18):1761-1767.
83. Hristov M, Heussen N, Schober A, Weber C. Intracoronary infusion of autologous bone marrow cells and left ventricular function after acute myocardial infarction: a meta-analysis. *J Cell Mol Med*. 2006;10(3):727-733.
84. Erbs S, Linke A, Adams V, et al. Transplantation

of blood-derived progenitor cells after recanalization of chronic coronary artery occlusion: first randomized and placebo-controlled study. *Circ Res*. 2005; 97(8):756-762.
85. Strauer BE, Brehm M, Zeus T, et al. Regeneration of human infarcted heart muscle by intracoronary autologous bone marrow cell transplantation in chronic coronary artery disease: the IACT Study. *J Am Coll Cardiol*. 2005;46(9):1651-1658.
86. Assmus B, Honold J, Schachinger V, et al. Transcoronary transplantation of progenitor cells after myocardial infarction. *N Engl J Med*. 2006;355(12):1222-1232.
87. Assmus B, Fischer-Rasokat U, Honold J, et al; TOPCARE-CHD Registry. Transcoronary transplantation of functionally competent BMCs is associated with a decrease in natriuretic peptide serum levels and improved survival of patients with chronic postinfarction heart failure: results of the TOPCARE-CHD Registry. *Circ Res*. 2007;100(8):1234-1241.
88. Perin EC, Dohmann HF, Borojevic R, et al. Improved exercise capacity and ischemia 6 and 12 months after transendocardial injection of autologous bone marrow mononuclear cells for ischemic cardiomyopathy. *Circulation*. 2004;110(11)(suppl 1):II213-II218.
89. Perin EC, Dohmann HF, Borojevic R, et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. *Circulation*. 2003;107(18):2294-2302.
90. Patel AN, Geffner L, Vina RF, et al. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: a prospective randomized study. *J Thorac Cardiovasc Surg*. 2005;130(6):1631-1638.
91. Hendrikx M, Hensen K, Clijsters C, et al. Recovery of regional but not global contractile function by the direct intramyocardial autologous bone marrow transplantation: results from a randomized controlled clinical trial. *Circulation*. 2006;114(1)(suppl): I101-I107.
92. Fuchs S, Kornowski R, Weisz G, et al. Safety and feasibility of transendocardial autologous bone marrow cell transplantation in patients with advanced heart disease. *Am J Cardiol*. 2006;97(6):823-829.
93. Beeres SL, Bax JJ, Dibbets-Schneider P, et al. Sustained effect of autologous bone marrow mononuclear cell injection in patients with refractory angina pectoris and chronic myocardial ischemia: twelve-month follow-up results. *Am Heart J*. 2006;152(4): 684.e11-6.
94. Gao LR, Wang ZG, Zhu ZM, et al. Effect of intracoronary transplantation of autologous bone marrow-derived mononuclear cells on outcomes of patients with refractory chronic heart failure secondary to ischemic cardiomyopathy. *Am J Cardiol*. 2006; 98(5):597-602.
95. Chen S, Liu Z, Tian N, et al. Intracoronary transplantation of autologous bone marrow mesenchymal stem cells for ischemic cardiomyopathy due to isolated chronic occluded left anterior descending artery. *J Invasive Cardiol*. 2006;18(11):552-556.
96. Manginas A, Goussetis E, Koutelou M, et al. Pilot study to evaluate the safety and feasibility of intracoronary CD133(+) and CD133(-) CD34(+) cell therapy in patients with nonviable anterior myocardial infarction. *Catheter Cardiovasc Interv*. 2007; 69(6):773-781.
97. Losordo DW, Schatz RA, White CJ, et al. Intramyocardial transplantation of autologous CD34+ stem cells for intractable angina: a phase I/IIa double-blind, randomized controlled trial. *Circulation*. 2007; 115(25):3165-3172.
98. Mocini D, Staibano M, Mele L, et al. Autologous bone marrow mononuclear cell transplantation in patients undergoing coronary artery bypass grafting. *Am Heart J*. 2006;151(1):192-197.
99. Stamm C, Kleine HD, Choi YH, et al. Intramyocardial delivery of CD133+ bone marrow cells and coronary artery bypass grafting for chronic ischemic heart disease: safety and efficacy studies. *J Thorac Cardiovasc Surg*. 2007;133(3):717-725.
100. Miyamoto K, Nishigami K, Nagaya N, et al. Unblinded pilot study of autologous transplantation of bone marrow mononuclear cells in patients with thromboangiitis obliterans. *Circulation*. 2006;114(24): 2679-2684.
101. Lenk K, Adams V, Lurz P, et al. Therapeutical potential of blood-derived progenitor cells in patients with peripheral arterial occlusive disease and critical limb ischaemia. *Eur Heart J*. 2005;26(18):1903-1909.
102. Bartsch T, Brehm M, Zeus T, Kögler G, Wernet P, Strauer BE. Transplantation of autologous mononuclear bone marrow stem cells in patients with peripheral arterial disease (the TAM-PAD study). *Clin Res Cardiol*. 2007;96(12):891-899.
103. Kim DI, Kim MJ, Joh JH, et al. Angiogenesis facilitated by autologous whole bone marrow stem cell transplantation for Buerger's disease. *Stem Cells*. 2006; 24(5):1194-1200.
104. Durdu S, Akar AR, Arat M, Sancak T, Eren NT, Ozyurda U. Autologous bone-marrow mononuclear cell implantation for patients with Rutherford grade II-III thromboangiitis obliterans. *J Vasc Surg*. 2006; 44(4):732-739.
105. Kawamura A, Horie T, Tsuda I, et al. Prevention of limb amputation in patients with limbs ulcers by autologous peripheral blood mononuclear cell implantation. *Ther Apher Dial*. 2005;9(1):59-63.
106. Tateishi-Yuyama E, Matsubara H, Murohara T, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet*. 2002;360(9331):427-435.
107. Saigawa T, Kato K, Ozawa T, et al. Clinical application of bone marrow implantation in patients with arteriosclerosis obliterans, and the association between efficacy and the number of implanted bone marrow cells. *Circ J*. 2004;68(12):1189-1193.
108. Ishida A, Ohya Y, Sakuda H, et al. Autologous peripheral blood mononuclear cell implantation for patients with peripheral arterial disease improves limb ischemia. *Circ J*. 2005;69(10):1260-1265.
109. Terai S, Ishikawa T, Omori K, et al. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells*. 2006;24(10):2292-2298.
110. Mohamadnejad M, Alimoghaddam K, Mohyeddin-Bonab M, et al. Phase 1 trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis. *Arch Iran Med*. 2007;10(4):459-466.
111. am Esch JS II, Knoefel WT, Klein M, et al. Portal application of autologous CD133+ bone marrow cells to the liver: a novel concept to support hepatic regeneration. *Stem Cells*. 2005;23(4):463-470.

