Emerging Treatment Options for Refractory Angina Pectoris: Ranolazine, Shock Wave Treatment, and Cell-Based Therapies

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A challenge of modern cardiovascular medicine is to find new, effective treatments for patients with refractory angina pectoris, a clinical condition characterized by severe angina despite optimal medical therapy. These patients are not candidates for surgical or percutaneous revascularization. Herein we review the most up-to-date information regarding the modern approach to the patient with refractory angina pectoris, from conventional medical management to new medications and shock wave therapy, focusing on the use of endothelial precursor cells (EPCs) in the treatment of this condition. Clinical limitations of the efficiency of conventional approaches justify the search for new therapeutic options. Regenerative medicine is considered the next step in the evolution of organ replacement therapy. It is driven largely by the same health needs as transplantation and replacement therapies, but it aims further than traditional approaches, such as cell-based therapy. Increasing knowledge of the role of circulating cells derived from bone marrow (EPCs) on cardiovascular homeostasis in physiologic and pathologic conditions has prompted the clinical use of these cells to relieve ischemia. The current state of therapeutic angiogenesis still leaves many questions unanswered. It is of paramount importance that the treatment is delivered safely. Direct intramyocardial and intracoronary administration has demonstrated acceptable safety profiles in early trials, and may represent a major advance over surgical thoracotomy. The combined efforts of bench and clinical researchers will ultimately answer the question of whether cell therapy is a suitable strategy for treatment of patients with refractory angina.

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KEY WORDS

Refractory angina pectoris • Stem cell therapy • Coronary artery disease

Although medical and surgical treatments often provide adequate solutions for individuals with coronary artery disease (CAD), an increasing need exists to develop treatment modalities for patients with angina who are unresponsive to maximal medical therapy, such as those with refractory angina pectoris. According to the European Society of Cardiology and the American College of Cardiology/American Heart Association, patients with refractory angina pectoris are described as having stable angina pectoris, the presence of CAD on a recently performed coronary angiogram, and, despite optimal conventional antianginal medical therapy (β-blockers, calcium antagonists, short- and long-acting nitrates), have severe angina and functional class III-IV heart failure according to the Canadian Cardiovascular Society classification (CCS). In addition, the patients are not candidates for conventional revascularization procedures such as coronary artery bypass grafting (CABG) or percutaneous coronary intervention.[1]

Available estimates suggest that refractory angina pectoris affects between 600,000 and 1.8 million people in the United States, with as many as 50,000 new cases each year.[2] Approximately 30,000 to 50,000 new cases per year are also estimated in continental Europe.[2] Despite a wide variation in methods used to derive population estimates, there is a general consensus that the incidence and prevalence of this condition will continue to rise across countries as CAD-related survival rates continue to increase and populations age.[3]

Conventional Management

Conventional pharmacologic treatments are aimed at reducing the oxygen demand by the myocardium and improving myocardial perfusion, which should lead to an improvement in cardiac function and relief from symptoms. Drugs such as nitrates, β-blockers, and calcium channel blockers are particularly useful.

Changes in lifestyle (smoking cessation, weight loss, and treatment of comorbidities such as diabetes and hypertension) are also warranted. Additive measures, such as lipid lowering, inhibition of platelet aggregation, and interference in the renin-angiotensin system have also become established treatments for stable angina pectoris.[3,4]

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New Perspectives in the Treatment of Refractory Angina Pectoris

Ranolazine

Ranolazine, approved by the US Food and Drug Administration in 2006, was the first specific novel medical therapy available for the treatment of chronic stable angina after the introduction of calcium channel blockers in the 1980s. Ranolazine is a proven antianginal agent that, unlike β-blockers, nitrates, or calcium channel blockers, does not affect either heart rate or blood pressure. Its mechanism of action is primarily due to its ability to influence the Na^+ and Ca^{2+} homeostasis in cardiomyocytes. Ranolazine's mechanism of action primarily involves inhibition of the late Na^+ flux. By this effect, ranolazine prevents intracellular calcium overload and its subsequent deleterious electrical and mechanical effects. Ranolazine attenuates the abnormally prolonged and dysfunctional myocardial contraction that increases myocardial oxygen demand and, at the same time, is thought to improve coronary blood flow and myocardial oxygen supply by optimizing diastolic function. Randomized clinical studies have been performed to test its ability to reduce angina symptoms. The medication is useful to ameliorate the symptoms, but a high percentage of patients still have thoracic pain despite optimal medical management.[5,6]

Shock Wave Therapy

Cardiac shock wave therapy (CSWT) is a novel, noninvasive intervention that may ameliorate myocardial ischemia and improve cardiac function. Early clinical trials showed that CSWT alleviated angina symptoms and improved cardiopulmonary performances in patients with myocardial ischemia. Increasing evidence indicates that CSWT may reduce ischemic burden and provide angina relief by promoting angiogenesis and revascularization in ischemic myocardium. Earlier in vivo animal studies and human clinical studies demonstrated that low-energy pulse waves produced by CSWT induced a "cavitation effect" of sorts (micron-sized violent bubble collapse within and outside cells), exerting a mechanical shear

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force on myocardial and vascular endothelial cells. Furthermore, improved regional myocardial blood flow and capillary density were also observed.

Clinical studies corroborated these early findings, as myocardial perfusion in ischemic regions was enhanced following CSWT. However, this treatment is effective in a minority of patients, and requires many applications, increasing the social costs.[5]

Cell Therapy in Refractory Ischemia

The clinical limitations of the efficiency of conventional approaches justify the search for new therapeutic options. Regenerative medicine is considered the next step in the evolution of organ replacement therapy. Its purpose is not just to replace the malfunctioning organs. It provides the elements required for in vivo repair, devises replacements that seamlessly integrate with the living body, and stimulates and supports the body's intrinsic capacities to regenerate and to heal. Increasing knowledge on the role of circulating cells deriving from bone marrow, called endothelial progenitor cells (EPCs), on cardiovascular homeostasis in physiologic and pathologic conditions has prompted the clinical use of these cells to relieve ischemia.[7]

Biology of EPCs

The discovery of bone marrow-derived EPCs circulating in the blood by Asahara and colleagues[8] in 1997 has resulted in a new paradigm for endothelial regeneration and introduced a potential new approach to the treatment of cardiovascular disease. EPCs are adult progenitor cells, which have the capacity to proliferate, migrate, and differentiate into endothelial cell lineage, but they have not yet acquired characteristics of mature endothelial cells.[9] These cells induce neovascularization through paracrine stimulation[10] and become incorporated in the wall of newly formed vessels when injected into animal models of hind limb ischemia (mice and rabbits). EPCs can be localized in adult bone marrow,[11] peripheral blood,[12,13] and human umbilical cord blood.[14-17] In adults, EPCs are thought to derive from the hemangioblast, and can be expanded ex vivo from $CD34^+/CD133^+/KDR^+/CD45^{+/-}$ cells. Stem cells that can be differentiated into EPCs exist in a quiescent state associated with bone marrow niches. In microenvironments EPCs can either remain in an undifferentiated and quiescent state or differentiate. Under physiologic conditions only a small number of these cells are maintained in peripheral circulation, where they contribute to endothelial and vascular homeostasis. In response to vascular injury or physiologic stress, EPCs can be mobilized from bone marrow and recruited to the damaged area. Increase of peripheral blood EPCs can be induced by a variety of signals from the periphery, including angiogenic growth factors (vascular endothelial growth factor-A, stromal cell-derived factor-1, granulocyte colony-stimulating factor [G-CSF]), cytokines (granulocyte-macrophage colony-stimulating factor), hormones (erythropoietin, estrogen), or drugs (statins), and home to areas of ischemic injury where they integrate into growing vessels. In fact, EPC levels are generally low in healthy subjects, decrease in chronic vascular disease, and transiently increase during acute vascular damage.[18] There is evidence that patients with cardiovascular risk factors (diabetes, hypertension, high cholesterol, smoking, obesity, and metabolic syndrome) have dysfunctional endothelial progenitors. In fact, their numbers are reduced in the circulation. They have a reduced migratory activity, impaired clonogenicity and survival and, thus, a reduced in vivo neovascularization capacity.

EPCs can be localized in adult bone marrow, peripheral blood, and human umbilical cord blood.

Role in Ischemia

The advantage of EPCs' therapeutic use depends on their ability to integrate into newly forming vessels or to activate neovascularization by paracrine mechanisms. The positive contribution of EPCs to adult neovascularization has been considered a useful approach in order to attenuate myocardial ischemia in CAD. One of the principal mechanisms of their framework appears to be the release of vasculoprotective molecules, such as nitric oxide (NO). In particular, the endothelial-specific NO synthase (eNOS) exerts pleiotropic cytoprotective effects in the vessel wall, reduces oxidative stress, modulates vascular tone and platelet adhesion, and impairs the development of atherosclerosis. It has been shown that EPCs overexpressing eNOS have an enhanced antiproliferative in vivo effect that significantly reduced the neointimal hyperplasia.[19] EPCs also exert a significant reduction in collagen deposition, apoptosis of cardiomyocytes, and cardiac remodeling.[20]

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Cell Type and Source in Clinical Practice

The observation that bone marrow elements contribute to cardiac repair in the ischemic heart served as the rationale for adult bone marrow cell therapy after an ischemic event. The evidence that precursors of endothelial cells exist within the mononuclear cell fraction of adult bone marrow forms the basis for the use of bone marrow mononuclear cells (BMMNCs) in clinical trials.[21] Because the numbers of autologous EPCs from peripheral blood or umbilical cord blood are limited, a great amount of attention has been directed to autologous whole BMMNCs.[5] Several investigators have chosen to deliver unfractionated BMMNCs, a technique that has the advantage of minimizing extensive ex vivo manipulation of the cells to isolate and expand a selected population of cells.[21] The potential disadvantage of delivering a mixture of cells is that the percentage of cells that are therapeutically useful may be small. A growing body of evidences suggests that $CD133^+$ could be a useful marker that identifies a more primitive human progenitor subpopulation compared with classical $CD34^+$. Moreover, in addition to hematopoiesis, $CD133^+$ cells have been shown to possess endothelial capacity.[22] Many reports from different groups[4,6,23] showed that intramyocardial delivery of purified $CD133^+$ cells is safe: if associated with CABG surgery, it provides beneficial effects; if used for refractory myocardial ischemia, it improves heart perfusion. From all these results we can conclude that $CD133^+$ cells could be a useful marker to select progenitor cells for a therapeutic purpose.

Many trials focused the attention on mobilizing cells from bone marrow by different regimens of growth factor stimulation. Although many cytokines have been used in preclinical models, at the clinical level, only G-CSF received sufficient priority. Use of this factor in patients is facilitated by its already available clinical approval to mobilize and collect hematopoietic stem cells for hematologic transplantation by apheresis.[3]

Routes of Administration

The optimal delivery route with regard to safety and efficacy remains to be established. Three primary routes of cell administration have been described: (1) retrograde via the coronary sinus, (2) anterograde intracoronary, and (3) intramyocardial (endocavitary/epicardial injections).

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Direct intramyocardial injection appears to be the most promising technique due to its ability to more closely target the ischemic territory of interest and, potentially, achieve the greatest local concentration of the therapeutic solution. The preferred strategy of intramyocardial cell administration took advantage of either fluoroscopic or NOGA®-guided endocavitary delivery (Cordis Corporation, East Bridgewater, NJ). Preliminary experiences also reported intramyocardial administration via the epicardial route under direct minithoracotomic surgical access after an accurate study of the electrophysiologic properties of the myocardium to assess the target area of ischemic but still viable myocardial tissue.

Overview From Clinical Trials

On the basis of encouraging results of preclinical studies, various clinical trials have been carried out in order to evaluate the safety and efficacy of cell therapy in patients with refractory ischemic cardiomyopathy, as shown in Table 1. The clinical experience of cell therapy in a setting of refractory ischemia currently encompasses approximately 250 patients, 120 involved in phase 1/2, and 130 in randomized controlled trials.

Tse and colleagues[24] conducted the first in-human study to evaluate the safety of intramyocardial transplantation of autologous BMMNCs for eight patients with intractable angina. Immediately before bone marrow cell injection, the NOGA system was used to perform electromechanical mapping of the left ventricle and then to guide the BMMNC injections to the area of ischemia. The absence of any acute procedural complications or long-term sequelae, including ventricular arrhythmia, myocardial damage, or development of intramyocardial tumor, provided a strong foundation for performing larger and more definitive trials. In most trials, EPCs were isolated from the total mononuclear cell population via magnetic positive selection of $CD34^+$ or $CD133^+$ cells. Although there was a limited number of patients included in the early trials, there was evidence suggesting an improvement in terms of clinical benefits and myocardial perfusion, and almost all reports have demonstrated acceptable safety profiles. Losordo and colleagues[14] performed a phase I/IIa, double-blind, placebo-controlled,

TABLE 1

Clinical Trials of Stem Cell Therapy in Refractory Angina

Study	Study Design (treated/control)	Cell Type	Delivery	Mean follow-up (mo)	Safety	Results
Tse et al[24]	Phase 1 (8)	BMMNCs	IM^{endo}	3	No AEs reported	↑perfusion ↓angina episodes
Vicario et al	Phase 1 (14)	BM-$CD31^+$ cells	IV	6	Chest pain during procedure (2)	↑perfusion, collateral vessels, QoL ↓CCS class
Briguori et al	Phase 1	BMMNCs	IM^{epi}	12	Acute AF 7 d postprocedure (1)	↑perfusion, LVEF, QoL ↓CCS class
Losordo et al	Phase 2, RCT (18/6)	mPB-$CD34^+$ cells	IM^{endo}	12	SAEs evenly distributed	↓CCS class, angina episodes
Tse et al	Phase 2, RCT (19/9)	BMMNCs	IM^{endo}	19	Carcinoma of the urinary bladder (1)	↑exercise time, LVEF ↓angina episodes
Babin-Ebell et al	Phase 1 (6)	BM-$CD133^+$ cells	IM^{epi}	6	No AEs reported	↓CCS class ↑LVEF
Gowdak et al	Phase 1 (8)	BMMNCs	IM^{epi}	6	No AEs reported	↓CCS class ↑perfusion
Kovacic et al	Phase 2 (36)	mPB-$CD133^+$ cells vs BMMNCs	IC	3	Cardiac ischemia (4), thrombocytopenia (2), gout (1)	↑perfusion ↓angina episodes
Pompilio et al	Phase 1 (5)	mPB vs BM-$CD133^+$ cells	IM^{epi}	24	No AEs reported	↓CCS class, angina episodes ↑perfusion
Jan Van Ramshort et al	Phase 2, RCT (25/25)	BMMNCs	IM^{epi}	3-6	Pericardial effusion postprocedure (1)	↓CCS class ↑LVEF, QoL
Reyes et al	Phase 1 (14)	BMMNCs	IM^{epi}	7	No AEs reported	↓CCS class
Hossne et al	Phase 1 (8)	BMMNCs	IM^{epi}	12-18	No AEs reported	↓CCS class ↑perfusion
Wang et al	Phase 2, RCT (56/56)	BM-$CD34^+$ cells	IC	6	No AEs reported	↓CCS class, angina episodes ↑perfusion
Lasala et al	Phase 1 (10)	BMMNCs vs BMMNCs	IC	6	No AEs reported	↑perfusion, LVEF, QoL
Tuma et al	Phase (14)	BMMNCs	IV	24	No AEs reported	↑perfusion, LVEF ↓angina episodes

AEs, adverse events; AF, atrial fibrillation; BM, bone marrow; BMMNCs, bone marrow mononuclear cells; CCS, Canadian Class Society; IC, intracoronary; IM^{endo}, endocardial intramyocardial delivery; IM^{epi}, epicardial intramyocardial delivery; IV, intravenous; LVEF, left ventricular ejection fraction; mPB, mobilized peripheral blood; QoL, quality of life; RCT, randomized controlled trials; SAE, serious adverse event.

dose-ranging trial to evaluate the intramyocardial transplantation of G-CSF-mobilized $CD34^+$ cells in 24 patients with intractable angina. Favorable trends in angina frequency, nitroglycerin usage, exercise tolerance, and perfusion defect were observed in patients administered with $CD34^+$ cells compared with patients who received placebo.

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Following these outcomes, a phase 2b study is currently underway in the United States. A recently published trial randomized 150 patients (1:1) to receive intracoronary transplantation of autologous bone marrow–derived $CD34^+$ cells. The target population included patients with CCS class III/IV heart failure who were refractory to medical treatment and not amenable to revascularization. Serious adverse events were comparable between cell and placebo groups. CCS class, exercise tolerance, and angina frequency appear to have improved in both groups at 3- and 6-month follow-up. However, the $CD34^+$ stem cell–treated group experienced a greater reduction of symptoms. More recently, a randomized, double-blind, placebo-controlled trial investigated the effect of intramyocardial bone marrow cell injection on myocardial perfusion and left ventricular function. In this trial, bone marrow cell injection resulted in a significant improvement in angina symptoms, quality of life, and exercise capacity, in line with precedent trials. The safety and efficacy of autologous endothelial progenitor cells $CD133^+$ for therapeutic angiogenesis (PROGENITOR trial) is currently ongoing in Spain and will provide more information regarding the potential benefit of $CD133^+$ cells to produce a clinically meaningful angiogenic response (ClinicalTrials.gov Identifier: NCT00694642).

Conclusions

The current state of therapeutic angiogenesis still leaves many questions unanswered. It is of paramount importance that the treatment is delivered safely. Direct intramyocardial and intracoronary administration has demonstrated acceptable safety profiles in early trials. Although therapeutic angiogenesis is not yet a part of routine therapy for refractory angina, it is crucial that we continue to learn from both encouraging and disappointing clinical and preclinical studies. The combined efforts of bench and clinical researchers will ultimately answer the question of whether cell therapy will be a suitable strategy for patients with refractory angina. ■

MAIN POINTS

- A challenge of modern cardiovascular medicine is to find new treatments for patients with refractory angina pectoris who are unresponsive to maximal medical therapy and who are not candidates for surgical or percutaneous revascularization.
- Ranolazine is a proven antianginal agent that, unlike β-blockers, nitrates, or calcium channel blockers, does not affect either heart rate or blood pressure. Ranolazine prevents intracellular calcium overload and its subsequent deleterious electrical and mechanical effects. It attenuates the abnormally prolonged and dysfunctional myocardial contraction that increases myocardial oxygen demand and, at the same time, is thought to improve coronary blood flow and myocardial oxygen supply by optimizing diastolic function.
- Cardiac shock wave therapy (CSWT) is a novel, noninvasive intervention that may ameliorate myocardial ischemia and improve cardiac function. Increasing evidence indicates that CSWT may reduce ischemic burden and provide angina relief by promoting angiogenesis and revascularization in ischemic myocardium.
- Regenerative medicine is considered the next step in the evolution of organ replacement therapy. It provides the elements required for in vivo repair, devises replacements that seamlessly integrate with the living body, and stimulates and supports the body's intrinsic capacities to regenerate and to heal. Increasing knowledge on the role of circulating cells deriving from bone marrow—called endothelial progenitor cells—on cardiovascular homeostasis in physiologic and pathologic conditions has prompted the clinical use of these cells to relieve ischemia.

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