Therapeutic Angiogenesis: The Pros and Cons and the Future

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ABSTRACT

Despite the improvements in medical, surgical and endovascular therapies, vascular disease is still a significant, critical clinical problem. The advances in understanding the mechanisms of neovascularization and the accumulated experiences of successful therapeutic application in animal models have raised expectations for therapeutic angiogenesis as a promising treatment option. However, the large, double-blinded, controlled clinical trials using therapeutic agent in the form of protein, naked DNA or viral gene therapy have failed to show clinical benefit. Nevertheless, by this time, cell based therapeutic angiogenesis has raised a promising option for the treatment of ischemic diseases. This article summarizes the essential preclinical research and major clinical trials on therapeutic angiogenesis, and it deals with several issues related to the failure of the clinical trials. Future directions in the realm of therapeutic angiogenesis are also described with focusing on cell based therapy.

KEY WORDS: Neovascularization; Angiogenesis; Clinical trial; Cell therapy.

Introduction

The advances in medical, surgical and endovascular therapy have improved the quality of life and prognosis of patients with ischemic disease, but there is a subset of so-called ‘no option patients’ who are refractory to these conventional therapies and they have a poor prognosis. Vascular disease is the still leading cause of mortality not only in western societies, but also in Korea. Elucidating the mechanisms of new blood vessel formation and the need for additional treatment options have raised the expectations of therapeutic angiogenesis as a promising treatment option. Strategies for therapeutic angiogenesis include delivering an angiogenic factor as a protein or a gene or cells that are vascular progenitors or they release angiogenic factors. These strategies have worked in animal studies and the early small-scale open labeled clinical trials. However, these approaches have failed to show clinical benefits in larger, double-blinded controlled clinical trials. Furthermore, uncontrolled angiogenesis has the potential to promote vascular proliferating disease like retinopathy and neoplastic disease, while inadequate angiogenesis can hasten atherosclerosis. The recent experimental and clinical trials using cell based therapy have showed promising therapeutic potential to augment neovascularization and functional improvement.

This article reviews some of our current understanding of the regulation of blood vessel growth and it summarizes the essential preclinical research and major clinical trials concerned with using molecular therapies for ischemic disease, in conjunction with reviewing several variables that might cause failure of clinical trials. The current status and future directions of cell based therapy in ischemic diseases are also described.

Mechanisms of Neovascularization

Deprivation of oxygen and nutrients limits tissue viability and function. The natural response to tissue ischemia includes the local up-regulation of angiogenic growth factors, coupled with the mobilization and recruitment of circulating cellular elements that facilitate the development of new vasculature. Neovascularization is the result of several processes, including angiogenesis, arteriogenesis and potentially vasculogenesis (Fig. 1).

The term angiogenesis describes the sprouting of new capillaries from postcapillary venules. In adults, this is stimulated mainly by tissue hypoxia via activation of the hypoxia-inducible factor (HIF)-1 expression. HIF-1 activates the transcription of numerous genes, including vascular endothelial growth factor (VEGF), VEGF receptors flt-1, neuropilin-1 and angiopoietin-2. Angiogenesis predominantly leads to the development of capillaries, and it does not seem to be effective in increasing the...
vasculogenesis will predominate at the sites of injury. In the case of a lethally irradiated mouse receiving a bone marrow transplant, the predominant process, with very little arteriogenesis taking place. However, in the case of a common femoral site of ligation, whereas angiogenesis will predominate with very little arteriogenesis. The initial trigger is hypoxia. C: arteriogenesis is induced after stenosis or occlusion of a major artery (indicated by the gray spot). Fluid shear stress, caused by altered blood flow (thick arrows) through pre-existing collateral anastomosis (slim arrows) serves as initial trigger. Growth of collaterals proceeds by remodeling of pre-existing arterioles. EPC: endothelial progenitor cells.

Fig. 1. Scheme showing neovascularization mechanisms. A: vasculogenesis: According to this idea, endothelial tubes are produced as a first step (a). Maturation to arterioles proceeds by the recruitment of smooth muscle cells or progenitors (b). B: angiogenesis describes the growth of capillaries from pre-existing vessels. It proceeds either by sprouting of endothelial cell or by intussusception. The initial trigger is hypoxia. C: arteriogenesis is induced after stenosis or occlusion of a major artery (indicated by the gray spot). Fluid shear stress, caused by altered blood flow (thick arrows) through pre-existing collateral anastomosis (slim arrows) serves as initial trigger. Growth of collaterals proceeds by remodeling of pre-existing arterioles. EPC: endothelial progenitor cells.

In many circumstances, the endogenous angiogenic response is not sufficient to fully meet the metabolic needs of the compromised tissues, and this causes symptoms of ischemia. Attempts to augment this natural revascularization response have been termed therapeutic angiogenesis and this has primary involved the administration of growth factors and more recently cellular products. The most commonly employed growth factors have been members of the VEGF and fibroblast growth factor (FGF) families. In addition, recent trials have involved hepatocyte growth factor (HGF) and HIF-1α. In all cases, the tested formulations were found to be effective in animal studies that typically employed young healthy animals. However, all the agents tested in the setting of double-blind, randomized clinical trials have uniformly failed to demonstrate efficacy.

Results of Preclinical Research as Pros

Preclinical studies have suggested a beneficial effect related to treatment with proangiogenic factors in animal models of acute ischemia. For example, dogs that underwent left coronary circumflex occlusion followed by intracoronary FGF-2 protein infusion showed a decreased infarct size, an increased number of collaterals and an increased capillary density within the distribution of the left circumflex artery. In rabbits, femoral artery excision followed by 10 days of intramuscular VEGF protein injection resulted in a dose-dependent improvement in the number of collaterals, the capillary density and hemodynamic improvement. Successful experimental results with animal models of therapeutic angiogenesis have encouraged the performance of clinical trials.

Results of Large Randomized Clinical Trials as Cons

In patients with coronary artery disease

Five large randomized, placebo-controlled trials of coronary angiogenesis have been reported to date (Table 1). The FGF2 initiating revascularization support trial (FIRST) recruited 337 chronic angina patients who were considered unsuitable for mechanical revascularization. The individuals were randomized to either a single intracoronary FGF2 (rFGF2) protein or placebo. Recombinant FGF2 did not improve exercise tolerance or myocardial perfusion, but the patients showed trends toward symptomatic improvement at 90 days as measured by the frequency score of Seattle angina questionnaire (SAQ). However this trend was not sustained at 180 days.

The VEGF in ischemia for vascular angiogenesis (VIVA) trial randomized 178 patients with stable angina to receive placebo or low dose (17 ng/kg/min) recombinant human VEGF (rhVEGF) or high dose (50 ng/kg/min) rhVEGF by an intracoronary infusion on day 0, followed by intravenous infusion on days 3, 6 and 9. After 120 days, the angina symptoms diminished, but no objective improvement was demonstrated by nuclear
perfusion or angiography.

The angiogenic gene therapy (AGENT) trial series investigated the efficacy of an intracoronary infusion of adenovirus encoding the FGF4 gene (Ad5.FGF4).\textsuperscript{16} AGENT1 randomized 79 patients with stable angina to receive single intracoronary doses of Ad5.FGF4. Interestingly, a statistically significant improvement in exercise tolerance was noted. The promising result of AGENT1 provided the rationale for AGENT2,\textsuperscript{17} which was a double-blind randomized trial designed to assess whether Ad5.FGF4 improved myocardial perfusion. There was a significant improvement in myocardial perfusion in the Ad5.FGF4 group. However, two large phase III trials, AGENT3 and AGENT4, did not demonstrate improvement in exercise tolerance in the Ad5.FGF4 groups compared to the controls.

The randomized evaluation of VEGF for angiogenesis in severe coronary disease (REVASC) trial randomized 67 no-option patients to receive injections of replication defective adenovirus containing the VEGF121 gene (AdVEGF121) throughout the free wall of the left ventricle via mini-thoracotomy or continuation of optimal medical therapy. Despite the improvements in exercise tolerance, there was no difference on the nuclear imaging between the two groups.

The Euroinject One trial randomized 80 no-option patients with severe ischemic heart disease to receive either 0.5 mg of VEGF165 plasmid or placebo plasmid targeted to the heart region that showed a stress-induced perfusion defect.\textsuperscript{18} Although VEGF gene transfer significantly improved the local wall motion abnormalities, perfusion defect did not significantly differ between the VEGF gene transfer and placebo groups (38 ± 3% and 44 ± 2%, respectively).

### In patients with peripheral artery disease

#### Patients with claudication

Two randomized, placebo-controlled trials have evaluated proangiogenic therapy in patients with claudication. The regional angiogenesis with vascular endothelial growth factor (RAVE) trial randomized 105 patients with unilateral exercise-limiting claudication to receive either intramuscular delivery of low dose (4 × 10\textsuperscript{7} particle units (PU)) or high dose (4 × 10\textsuperscript{10} PU) Ad.VEGF121 or placebo.\textsuperscript{19} The primary end point was the change in the peak walking time (PWT) at 12 weeks, but this did not differ among the low dose (1.6 ± 1.9 minutes), high dose (1.5 ± 1.1 minutes) and placebo (1.8 ± 3.2 minutes) groups.

The therapeutic angiogenesis with recombinant fibroblast growth factor for intermittent claudication (TRAFFIC) trial randomly assigned 187 patients with infrainguinal atherosclerosis and claudication to either single or double dose bilateral intra-arterial infusions of rFGF2 or pla-

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**Table 1. Summary of large, randomized, placebo controlled clinical trials of therapeutic angiogenesis**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>N</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRST</td>
<td>Chronic angina</td>
<td>337</td>
<td>Intracoronary FGF, with dose escalation</td>
<td>ETT</td>
<td>Improved angina at 90 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Angina questionnaire</td>
<td>No significant improvement in the primary endpoints at 180 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nuclear perfusion imaging QOL</td>
<td>No significant improvement for the other endpoints</td>
</tr>
<tr>
<td>VIVA</td>
<td>Chronic angina</td>
<td>178</td>
<td>Intracoronary VEGF (low dose, high dose) on days 0, 3, 6 and 9 vs. placebo</td>
<td>Myocardial perfusion imaging ETT</td>
<td>Improved angina at 120 days with high dose VEGF treatment</td>
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<tr>
<td></td>
<td>ineligible for</td>
<td></td>
<td></td>
<td>Angina questionnaire QOL</td>
<td>No significant improvement</td>
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<td>standard</td>
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<tr>
<td></td>
<td>revascularization</td>
<td></td>
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</tr>
<tr>
<td>AGENT</td>
<td>Chronic angina with</td>
<td>79</td>
<td>Intracoronary adenoviral FGF with dose escalation</td>
<td>ETT</td>
<td>Improved ETT in a subgroup of baseline ETT 10 min</td>
</tr>
<tr>
<td></td>
<td>ETT of 3 minutes</td>
<td></td>
<td></td>
<td>Stress echocardiography Angina onset</td>
<td>Otherwise no difference between the groups</td>
</tr>
<tr>
<td>REVASC</td>
<td>Severely symptomatic</td>
<td>67</td>
<td>AdVEGF121 (4 × 10\textsuperscript{10} particle units [pu]) in 30 × 100 microliters (mCL) direct intramyocardial injections throughout the free wall of the left ventricle via a minithoracotomy</td>
<td>ETT time to additional 1-mm ST segment depression</td>
<td>Significant improvement in the AdVEGF121 group compared with the control group at week 26 (p=0.024), but not at week 12 (p=0.356)</td>
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<tr>
<td></td>
<td>CAD who were not</td>
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<td></td>
<td>candidates for</td>
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<tr>
<td></td>
<td>conventional</td>
<td></td>
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<tr>
<td></td>
<td>revascularization</td>
<td></td>
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</tr>
<tr>
<td>Euroinject one</td>
<td>Chronic angina</td>
<td>80</td>
<td>Intramyocardial VEGF plasmid to ischemic myocardium vs. placebo</td>
<td>Myocardial perfusion Wall motion Angina Exercise capacity</td>
<td>Improved wall motion abnormalities No significant difference in all other endpoints</td>
</tr>
<tr>
<td></td>
<td>ineligible for</td>
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<td>standard</td>
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<td></td>
<td>revascularization</td>
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Improvements in the peak walking time were observed at 180 days, but these improvements were insignificant when compared with the continued improvements in the placebo group.

**Patients with critical limb ischemia**

This randomized, placebo-controlled trial was conducted to evaluate intramuscular injections of plasmid VEGF specifically in diabetic patients with critical limb ischemia. Fifty-four patients were randomized to receive either an intramuscular VEGF plasmid injection twice over 4 weeks or placebo. The primary endpoint was major amputations, and this numbered 11% in the treatment group and 22% in the placebo group, but this difference did not reach statistical significance.

**Issues regarding clinical trials on therapeutic angiogenesis**

Assuming that therapeutic angiogenesis is valid, the discrepancies between the results of animal studies and the clinical studies raise a number of issues that might influence the results. Several issues we should reconsider include population selection and the placebo effect, the choice of a biological agent and its pharmacokinetics, monitoring and assessment of angiogenesis, and the safety and mode of delivery of the therapeutic agent.

**Population selection and placebo effect**

The individuals enrolled in the early phase clinical trials were typically no-option patients. These patients had a tendency to be older, to suffer from more extensive disease and they were refractory to maximized conventional therapies. These characteristics could make these patients poor candidates for angiogenesis; however, it is difficult to enroll a less severely affected population because both the government and local institutional review boards are reluctant to permit enrollment of patients into experimental gene therapy protocols when standard options are available. A partial solution to this problem will be the availability of biomarkers that can discern those patients who will have favorable angiogenic response, yet no such markers have been found to date. Another issue that might be related with the confusing results of the early clinical trials is the occurrence of a significant placebo response. Improvement of functional capacity, the symptoms and the pill counts were also found in the placebo group. Interestingly, symptomatic benefit in the placebo groups was frequently associated with significant improvement in the hard end points such as myocardial perfusion and function.

**Choice of therapeutic agent and the pharmacokinetics**

Selection of the biologic agents used in clinical trials has largely been based on their availability for a study or the intellectual property rights rather than on physiologic rationale. There have been tendency to make the choice at a time when it seemed that anything would work. The rationale for choosing biological agents should be thoroughly considered. Because arteriogenesis is far more potent than is angiogenesis in restoring blood flow to tissues that are compromised by a flow limiting lesion, the primary ability of agents would be better focused on the development of large arterial trunks. Because blood vessel growth is a complex event, it may be more effective to use multiple growth factors acting at different times and at different site. For example, coinadministration of VEGF and FGF2 exerts a synergistic angiogenic effect and the resultant vessels are less leaky. Once an effective agent have been identified, the next challenging issue is to develop an administration strategy that provides the necessary concentration of the agent at a desired location for an amount of time that’s sufficient not only to induce new vessel growth, but also to allow for their maturation (4 to 6 weeks or potentially longer). A slow-release gel formulation or more long-lived gene transfer vectors such as lentivirus will be an option. The remaining options include the systemic administration of an agent that specifically acts only in the desired organ or tissue. For example, placental growth factor (PIGF) appears to induce vessel growth only in the setting of ischemia. If this observation is correct, then a prolonged systemic administration of PIGF (e.g., by means of a wearable subcutaneous-injection minipump) may be another option.

**Monitoring and assessment of angiogenesis**

The ability to monitor the effect of angiogenic therapy has been a long-standing issue. In principle, this can be accomplished by either directly monitoring blood vessel growth or observing the functional effects of therapy. It is possible that single photon emission computerized tomography (SPECT) imaging does not show the benefits of angiogenic therapy because the technique is simply not sensitive enough. Molecular imaging of angiogenesis has recently received prominent attention, with a number of reports demonstrating the feasibility of observing blood vessel growth in tissues by targeting several “angiogenic” endothelial cell-specific antigens such as VEGF receptor 2 or CD105 (endoglin). Although such studies are clearly intriguing, none of the approaches has been applied in clinical trials. Another alternative is direct visualization of new vasculature. A particularly interesting technology is the 3D reconstruction of tomographic images. Finally, magnetic resonance angiography can also provide visualization of collaterals. Although relatively effective in the limb, the sensitivity of MRI coronary reconstruction is not yet sufficient. Positron-emission tomography (PET) and MRI are the main alternatives to SPECT imaging. PET boasts of somewhat higher spatial resolution, elimination of attenuation and the quantitative assessment of perfusion. However, the experience...
with PET in clinical coronary artery disease trials is limited, and no large angiogenesis trial to date has used PET as an end point. There is more experience with MRI for perfusion and cardiac function assessment, but even here no agreement has been reached with regard to how these factors should be measured. 283

Safety issues for therapeutic angiogenesis

Therapies to enhance localized neoangiogenesis in the ischemic myocardium have raised several safety issues.

Nontarget tissue neovascularization

The potential risks of non target tissue neovascularization include proliferative retinopathy, acceleration of atherosclerosis and occult tumor growth.

There was one report about accelerated tumor growth of preexisting malignancy, which evokes the need for rigorous screening for occult malignancy prior to initiating any angiogenic therapy. Yet there was no clear evidence that exogenous angiogenic factor induces de novo malignancy.

Atherosclerotic plaque growth and vulnerability

Intraplaque angiogenesis and its possible role in atherosclerosis are the subjects of much debate. Several studies have suggested that circulating endothelial progenitor cells play an important role in post injury reendothelialization, 2930 and that infusion of these cells or the stimulation of their release by angiogenic growth factors can promote a reduction in restenosis. 1012

On the other hand, systemic VEGF administration in atherosclerotic mice and rabbits was reported to promote atherosclerotic plaque growth, presumably by inducing vessel wall angiogenesis. 13 Intracoronary infusion of granulocyte-colony stimulating factor-mobilized peripheral blood endothelial progenitor cells in the setting of acute myocardial infarction resulted in a marked increase of in-stent restenosis. 34

Mode of therapeutic agent delivery

The requirements for delivery are accurate targeting the desired location, effective deposition of the agent and adequate maintenance of the agent’s half life to achieve the optimal biologic effect. Tissue or cell specific targeting of gene delivery vectors is under development to enhance the specificity of gene transfer.

Intracoronary approach

Although this approach is easily accessible and its efficacy has been repeatedly proven in numerous preclinical models, several clinical studies reported its low efficacy. 35 This approach is particularly unsuitable for adenoviral gene therapy because very few viruses can traverse the normal endothelial barrier.

Intrapericardial approach

Despite efficient delivery into the pericardium and epicardium, only minimal therapeutic benefit has been achieved because permeation into the endocardium where the arterioles terminate and into new vessels is restricted.

Intramycocardial or endomyocardial transfer

The intramyocardial transfer of gene or protein facilitates a more targeted approach and this can be performed percutaneously or in conjunction with a thoracotomy. Endomyocardial local delivery with real time magnetic resonance guidance has been reported with promising results. 36

Table 2. Summary of the major clinical trials to assess cell-based therapy in patients with acute myocardial infarction

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>N</th>
<th>Days after AMI</th>
<th>Cell type</th>
<th>Safety</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOPCARE-AMI 40</td>
<td>59</td>
<td>4.9</td>
<td>CPC (n=30) BMC (n=29)</td>
<td>Safe</td>
<td>Global contractility ↑ (LVA/MRI) End systolic volume ↓ (LVA/MRI) Viability ↑ (MRI) Flow reserve ↑ (Doppler) Global contractility ↑ (LVA) 6 months: global contractility ↑ (MRI) 18 months: no significant difference (MRI) 18 months: diastolic dysfunction ↓ (Echo) Global contractility no change Infarct size ↓ (MRI) Global contractility no change Global contractility ↑ (LVA) Adverse remodelling ↓ Clinical outcome ↑</td>
</tr>
<tr>
<td>Chen et al 42</td>
<td>69</td>
<td>18</td>
<td>BMSC (n=34) vs control (n=35)</td>
<td>Safe</td>
<td></td>
</tr>
<tr>
<td>BOOST 43</td>
<td>60</td>
<td>4.8</td>
<td>BMC vs control 1:1 randomized</td>
<td>Safe</td>
<td></td>
</tr>
<tr>
<td>Janssens et al 44</td>
<td>67</td>
<td>&lt;1</td>
<td>BMC vs placebo 1:1 randomized</td>
<td>Safe</td>
<td></td>
</tr>
<tr>
<td>ASTAMI 45</td>
<td>100</td>
<td>6</td>
<td>BMC vs control 1:1 randomized</td>
<td>Safe</td>
<td></td>
</tr>
<tr>
<td>REPAIR-AMI 46</td>
<td>204</td>
<td>4</td>
<td>BMC vs placebo 1:1 randomized</td>
<td>Safe</td>
<td></td>
</tr>
</tbody>
</table>

TOPCARE-AMI: transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction, CPC: circulating progenitor cell, BMC: bone marrow derived cell, LVA: left ventricular angiography, BMSC: bone marrow mesenchymal stem cell, Echo: echocardiography, BOOST: bone marrow transfer to enhance ST elevation infarct regeneration, ASTAMI: autologous stem-cell transplantation in acute myocardial infarction, REPAIR: reinfusion of enriched progenitors cells and infarct remodelling.
Future Directions

Advances in our understanding of the mechanisms of neovascularization and the favorable results of several experimental and clinical studies using stem or progenitor cells suggests that cell-based therapy may play a critical role in revascularization and has promising therapeutic potential.

The cell types known to have therapeutic potential comprise at least three different groups: the bone marrow-derived stem cells, the circulating pool of stem or progenitor cells, which, at least in part, are derived from the bone marrow, and the tissue-resident stem cells.

A variety of autologous adult progenitor cells are currently undergoing preclinical evaluation. Clinically, bone marrow is presently the most frequent cell source used for cardiac repair because there are more than 30 years of clinical experience using these cells and the safety profile of bone marrow-derived mononuclear cells is excellent. Circulating progenitor cells that participate in postnatal revascularization have been termed EPCs, which are characterized by the expression of both hematopoietic stem cell markers (CD133+ or CD34+) and endothelial marker VEGF-receptor 2. There are more than two different types of EPCs that might play different roles in adult neovascularization. These cells are mobilized from the bone marrow compartment and they are recruited to sites of ischemia. EPCs can coordinate neovascularization by paracrine effects, transdifferentiation into endothelial cells, pericytes or smooth muscle cells, and the stabilization of vascular networks. Dysfunction of circulating EPCs in patients with chronic renal failure might be related to progression of cardiovascular disease. A subset of mononuclear cells derived from cord blood cells seems to have the potential to differentiate into EPCs. Other stem cells that have therapeutic potential include both the mesenchymal and endothelial progenitor cells derived from adipose tissue, and the cardiac stem cells that reside in different tissues.

Despite the uncertainty about how these cells exert their effect, there have been clinical trials to assess the safety and efficacy of bone marrow derived cells in patients with acute myocardial infarction (Table 2). Most of the studies suggested that cell therapy reduced the infarct size and improved the cardiac contractile function. No major safety concerns were raised during the initial clinical trials, although several potential side effects need to be carefully monitored. However, cell therapy is still in its early stages, so many of the similar unanswered questions from previous proangiogenic treatments are still relevant. For example, issues about identifying those patients who would benefit most from cell therapy, the optimal cell type and the number of these cells for patient with acute and chronic diseases, and the best time and mode of cell delivery need to be further evaluated.

Clearly, the use of stem/progenitor cells for cardiac repair is currently not at a stage to be used in routine clinical practice. Nevertheless clinical trials with the highest scientific and ethical standards, in conjunction with further extensive in vitro and animal studies, will offer novel opportunities to fulfill the clinical need of treating patients with severe cardiac dysfunction.

Conclusion

Although advances in the understanding of the molecular mechanisms of neovascularization and the successful results of animal experiments have encouraged us to realize the potential of molecular therapy for treating ischemic disease, the large randomized clinical experiences using single agent infusion or gene therapy have been disappointing. However, we learned many lessons from the previous experiences about the choice of therapeutic agent, the effective delivery modality, proper patient selection and the methods of monitoring treatment efficacy. The recent efforts using cell based therapies have given physicians a promising option to treat ischemic disease, although we are still in need of more preclinical and clinical data. There are still many reasons to be optimistic about the eventual success of therapeutic angiogenesis.

REFERENCES


