Therapeutic Myocardial Angiogenesis Via Vascular Endothelial Growth Factor Gene Therapy Moving on Down the Road

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mid the criticisms levied at gene therapy researchers recently, the positive (yet preliminary) advances in therapies designed to elicit angiogenesis for the treatment of ischemic vascular disease, such as the current report by Vale and colleagues,1 are a breath of fresh air for cardiovascular specialists and their patients. Although therapeutic angiogenesis is still in its nascent stages (and its benefits unproven), the contrarian tactics employed by this group are reaping dividends. Whereas the standard approach of gene therapists has been to use viral-based vectors to treat otherwise lethal diseases, the scientists attempting to evoke therapeutic angiogenesis in this report chose to treat patients in whom the benefits may be primarily symptomatic, and they used a relatively low-tech, non–viral-based delivery system.

The notion that collateral circulation can protect ischemic tissues is not new; it dates back to the observations of early angiographers, who discovered that patients with severe coronary artery disease and preserved ventricular function frequently formed networks of collateral vessels. However, the ability to augment collateral vessel formation awaited the discovery of specific angiogenic factors. Several groups embraced the idea that angiogenic factors, such as vascular endothelial growth factor (VEGF), could be harnessed to improve the perfusion of ischemic tissues. Indeed, early animal studies were promising, demonstrating that recombinant VEGF administered intravenously enhanced collateral formation in ischemic tissues.2,3

Demonstrating that a single injection of VEGF was effective provided a proof-of-principle experiment. However, it was unclear whether this strategy would be translatable to humans given the differences in the pharmacodynamics and pharmacokinetics of these growth factors and the complexity added by the presence of underlying atherosclerosis in human patients. Some investigators chose to modulate the delivery of angiogenic proteins so that their effects were concentrated and sustained, for example, by intrapericardial delivery.4 Others, including the group led by Jeffrey Isner (which authored the current report1), reasoned that a gene transfer approach would be the best means to deliver angiogenic factors.

Ischemic vascular diseases are unique among the illnesses that have been chosen as targets for gene therapy. In contrast to genetic and malignant diseases and HIV infection—for which gene therapy is envisioned as a cure—vascular diseases are not inexorably lethal, and new therapies must first succeed by providing relief from discomfort and debilitation. Improvements in mortality, although desirable, are not necessary for a therapy to be considered successful, nor are such results even expected. Given this conundrum, the method used to deliver an angiogenic protein must meet rigorous expectations of safety. This may be the primary reason the Isner group chose plasmids as a means to deliver the VEGF gene.

Plasmids (small, circular pieces of DNA) are relatively nontoxic when used for gene transfer. However, this favorable safety profile comes at a cost in comparison with viral-based gene delivery methods. Plasmids are taken up inefficiently by most cells and are unprotected against cellular surveillance systems. Conventional wisdom has maintained that proteins expressed by plasmids would appear transiently and in few cells. For these reasons, only a small minority of Food and Drug Administration–approved gene therapy trials have used plasmids as gene delivery devices.

Although bucking conventional wisdom may have played some role in the Isner group’s decision to use an out-of-favor vector, the decision was not without a practical basis. First, striated muscle is unique among all tissues in its capacity to incorporate and express plasmids for periods measured in weeks.5 Second, VEGF is a secreted protein; the effects of VEGF secreted from one cell can be transmitted to adjacent cells, even if these cells have not themselves incorporated the VEGF plasmid. Finally, small changes in the local concentration of VEGF can have profound effects on its biological activity. Although the use of a plasmid-based system set the Isner group apart from most investigators flocking to the field of gene therapy, even skeptics must recognize that the decision was based on sound principles.

Having bet on a well-founded, albeit atypical, approach to treat vascular disease, the Isner group had to prove that the VEGF plasmid actually worked. In a rabbit model, they showed that an intramuscular injection of VEGF plasmid increased capillary formation and improved perfusion to ischemic limbs.6 VEGF expression was detectable for 14 days

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after injection, and (quite fortuitously) uptake of the plasmid was higher in ischemic compared with nonischemic muscles. These studies provided the basis for the first clinical gene therapy trials designed to elicit therapeutic angiogenesis.

Two phase I trials have been initiated to establish the safety of the VEGF plasmid in humans. One protocol examines the effects of VEGF injection into the ischemic muscles of patients with critical limb ischemia.7 Despite only transient increases in measurable VEGF levels, collateral vessel formation was documented in 7 of 10 treated limbs, improved distal blood flow in 8 of 10 limbs, and improvement in clinical status in 5 of 10 limbs. No side effects other than transient limb edema have been reported to date. Although the uncontrolled nature of these studies prevents drawing conclusions regarding the clinical utility of VEGF plasmid, they demonstrate the feasibility of this minimally invasive therapy for treating peripheral vascular disease.

A second protocol was initiated by the Isner group to examine the activity of VEGF plasmid administration as a treatment for patients with myocardial ischemia. This trial took observers by surprise because (1) few animal data existed to support this method and (2) myocardial plasmid injection requires general anesthesia and a minithoracotomy, thus making this trial among the most invasive of gene therapy trials yet initiated. Patients with class 3 or 4 angina had the VEGF plasmid directly injected into the myocardium via a lateral thoracotomy.8 In the first 5 patients to undergo this procedure, no operative complications occurred, and all 5 had an improvement in symptoms and in myocardial perfusion, as measured by single photon emission computed tomography (SPECT) imaging.

It is worth recognizing the similarities that exist between VEGF plasmid administration and another invasive procedure for treating myocardial ischemia, transmyocardial laser revascularization. Although angiogenic gene therapy for myocardial ischemia is at a much earlier stage in its development, it shares potential drawbacks with transmyocardial laser revascularization. In particular, the invasive approach is certain to be accompanied by some degree of morbidity and mortality, which must be weighed against a benefit that might not include a survival advantage, and repeated treatments using the thoracotomy approach will be impractical. In fact, the precise benefit derived from the myocardial angiogenesis procedure as described may be impossible to determine, because the invasiveness of the method has caused the Food and Drug Administration to preclude randomization against placebo.8

With these issues in mind, it is worthwhile to consider the report by Vale et al,1 which describes 13 additional patients enrolled in the Isner group’s myocardial angiogenesis trial. Objective evidence of improved myocardial perfusion was provided by SPECT imaging and by the technique of electromechanical mapping (EMM).9 Although this is a phase I, nonrandomized trial, the present report provides further data demonstrating symptomatic improvement in patients receiving intramyocardial VEGF plasmid injections. In addition, the investigators found that VEGF plasmid therapy reduced the amount of hibernating myocardium identified by electromechanical uncoupling (preserved electrical activity in areas of diminished local shortening) 60 days after gene therapy, an effect that correlated with changes in perfusion measured noninvasively by SPECT.1

Why might clinicians and other investigators be excited by these data? Previous studies in humans have shown that EMM discriminates between reversible and fixed myocardial perfusion defects in a manner similar to perfusion imaging.10 Vale et al1 propose that EMM provides objective evidence that VEGF plasmid improves perfusion to the myocardium. However, the additional evidence provided by EMM (an invasive percutaneous procedure) over that provided by noninvasive studies in the analysis of myocardial viability is yet to be determined.11

In fact, although EMM may be useful during this developmental phase of angiogenic therapy, it makes little sense to use EMM routinely as a diagnostic tool for myocardial viability unless it will be performed in conjunction with another invasive diagnostic or therapeutic procedure. In this regard, the study of Vale et al1 might seem mainly an experimental curio. However, if one accepts the premise that requiring a thoracotomy to deliver gene therapy will limit its broad applicability, then the present study can be viewed instead as an necessary first step in the transition toward a totally percutaneous myocardial gene therapy. EMM can serve as a method to determine the extent and location of myocardial ischemia in real time and also to direct the injection of VEGF plasmid (or another gene therapy tool) to improve myocardial viability. Indeed, a single case demonstrating such an application for EMM has been reported by this same group.12 An entirely percutaneous procedure should make considerably more sense to skeptics of the surgical approach and should increase the pool of patients who could benefit from myocardial VEGF therapy, particularly if the benefits of myocardial angiogenesis remain purely symptomatic.

Although our discussion has focused on the delivery of VEGF plasmid to elicit myocardial angiogenesis, this is not the only gene therapy approach being explored. A phase I study assessing the effects of intramyocardial injection of an adenoviral vector expressing VEGF, delivered either at the time of bypass or directly via thoracotomy, has been reported by an independent group, with similarly preliminary but favorable results.13 Trials involving other angiogenic factors and delivery methods are also in progress. Although we are still a long way from seeing gene therapy for myocardial ischemia delivered outside of experimental studies, the progress of the major groups in this field is extraordinary given the slow progress of gene therapy in other fields. In light of this, it is worth considering some fundamental questions that have yet to be answered by the reported data.

1. Are proposed gene therapies for myocardial angiogenesis safe? In the limited patient populations that have been reported, short-term safety profiles for these therapies are promising,6,13 although invasive delivery methods are certain to have attendant complications. The relatively short half-life of these therapies may minimize long-term consequences, such as retinopathy and tumor growth.

2. How does VEGF gene therapy work? The studies in progress are based on the hypothesis that VEGF will elicit
growth of new blood vessels to improve perfusion to ischemic tissues. The patients reported to date have shown improvements in Rentrop scores of collateralization.\textsuperscript{8,13} Whether these changes represent new vessel formation or the recruitment of existing collaterals is not clear, nor do we even know whether the effects seen so far are due to VEGF expression or to the effects of the intramuscular injection itself. We should keep in mind that VEGF can have effects (such as increased nitric oxide production\textsuperscript{14}) that may improve myocardial perfusion independently of angiogenesis.

3. Who will benefit from VEGF gene therapy? If VEGF gene therapy is superior to placebo in patients with myocardial ischemia (an issue far from being resolved), it will be interesting to see whether the effects are primarily symptomatic or whether a survival advantage is conferred. If therapeutic angiogenesis produces a survival benefit, its applications will obviously expand enormously in patients with severe coronary artery disease. In addition, it is quite possible that VEGF gene therapy, if deliverable by relatively noninvasive means (such as by EMM-guided percutaneous approaches), might be beneficial to patients with milder forms of coronary artery disease, perhaps in a fashion complementary with other interventional procedures. Such optimism must be tempered by the fact that the field of therapeutic angiogenesis is only now passing out of its infancy. We must still anticipate a rocky adolescence, and clinical implementation of these approaches is not likely to occur soon.

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