Myoblast Transplantation for MI and CHF Treatment

Cell- and gene-based therapies show promise in treating cardiovascular disease.

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Cell- and gene-based therapies hold tremendous potential to treat cardiovascular disease, however, significant obstacles need to be overcome before potential benefits are realized. There is no doubt that intracoronary or direct injection of either cells or genes into small animal models (mouse, rat, hamster, or rabbit) for heart disease produces improvements in cardiac function.[1] The challenges, however, to treat human heart disease are far greater than in experimental animal systems. Key among the challenges is the mode of delivery for the therapeutic agent. For the purposes of this review, we will focus on cell-based therapies, however, most of the conclusions can be generalized to gene therapy applications as well.

CHOICE OF THERAPEUTIC CELL

An array of different cell types have been used in animal models and in preliminary human clinical trials, and several comprehensive reviews detail recent progress in this area.[2,3] The ultimate effectiveness of any cell therapy will have to be demonstrated in well-controlled human clinical studies. From the accumulated knowledge to date in the emerging specialty of cell therapy, we can state several criteria that must be met to achieve success: (1) the cell population used needs to be prepared under controlled, well-defined procedures that guarantee consistent, viable cell isolates; (2) sufficient numbers of cells need to be delivered to or make their way to the site of damage; (3) cells must provide for sufficient repair and remodeling to sustain long-term (not just transient) recovery; (4) a reasonable cell dose based on the size of the infarct to be treated needs to be established; and (5) the fate of the cells injected needs to be determined (ie, where do the cells go and what do they become?). With these criteria in mind, we have chosen autologous skeletal myoblasts as the ideal cells for cardiac repair. Extensive experimentation in multiple labs around the world has repeatedly shown that autologous skeletal myoblasts can be consistently isolated and expanded *in vitro*, survive in both acute and chronic injury models, engraft and repair damaged myocardium in a predictable manner proportionate to the cell dose delivered, are safe, and provide for long-term benefit.[2,4]

METHOD OF INJECTION

There have been conflicting reports regarding the effectiveness of different routes of cell administration. The method that delivers the greatest consistency and reliability is direct injection into the heart muscle during an open chest procedure under visual guidance.[5-9] Both the location of the infarct and confirmation of successful injection are best ensured by direct visualization. However, an open heart procedure is not the most practical method for injection of cells. Initially, the treatment would be limited to patients already undergoing an open heart procedure, and benefits due to the cell transplant would be difficult to separate from the effects of concomitant procedures, which has been the experience in several clinical studies using direct

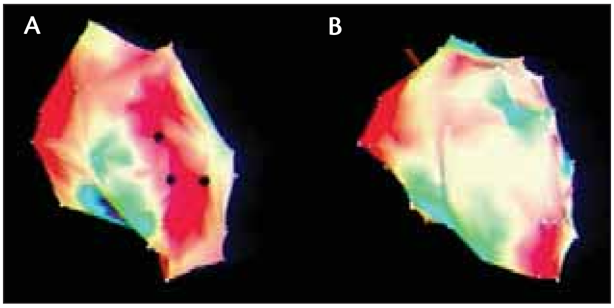

Figure 1. Baseline 3D unipolar voltage map (A). The red area demonstrates low voltage consistent with myocardial infarction. Three months after myoblast transplantation, normal voltage reflecting survival of myoblast is demonstrated (B).

TABLE 1. MYOCARDIAL INJECTION CATHETERS

Catheter Injection System	Description/Characteristics	References
Cordis MyoStar	3D mapping capability	11, 12, 14, 20, 21
Boston Scientific Stiletto	Standard injection	19, 22
Biocardia Morph-Helical	Corkscrew tip on injection needle for enhanced stability during injection	10, 15
Bioheart MyoCath	Standard injection	23, 24
Transvascular Trans-Accesss	Transvenous delivery system	25, 26

injection of cells into the surface of the heart. All of these studies have shown significant patient improvements, but it has been difficult to ascribe those improvements to the engraftment of the cells.[5-9] Any future studies would have to be designed to control for improvements due to concomitant procedures. Furthermore, fewer patients undergo open heart procedures, severely restricting the number of patients eligible to benefit from such a therapy. Some alternate forms of cell delivery, such as intracoronary, intravenous, or endocardial injection, would be to a greater extent more practical and applicable for a much larger population of patients.

For any cell therapy to be effective, adequate numbers of cells must be delivered to the site of damage and the delivery of those cells must be repeatable and safe. Endocardial delivery of cells has consistently been shown to be a safe and effective way to deliver cells to an infarct.[10-15] Intravenous delivery, although convenient and rapid, suffers from low efficiency of delivery to the specific site of damage. Cell-tracking studies show that a barely detectible number of cells find their way to the site of damage in the heart after intravenous administration, with the majority of the cells trafficking to the spleen and lungs.[16] Likewise, intracoronary delivery suffers from poor efficiency of cell delivery, although results show efficiencies greater than that achieved through the intravenous route. Intracoronary delivery, however, presents safety concerns for the recipient in some instances. Studies have shown the potential for microembolization in the coronary circulation created by cells too large to pass into the venous system.[17] In such cases, the cells could actually cause damage in addition to the infarct they were intended to treat. Because the potential for microembolization is dependent on the cells that are delivered, the potential risks and benefits for a particular cell type and mode of delivery will need to be tested empirically. Endoventricular cell delivery, unlike intravenous or intracoronary, provides safe, targeted and the highest efficiency of cell delivery to the area of infarct.[18] Although repeated studies have shown that intraventricular delivery is a safe and effective means for cell delivery, not all injection catheter systems are as equally safe and effective.

CATHETER INJECTION METHODS

There are now multiple options for the intraventricular injection of cells or gene therapy agents (Table 1). All of them have been shown effective in animal studies, but compatibility issues between catheters and the agent being delivered have been observed.[19] Therefore, caution is warranted before choosing a catheter system. The best option is to conduct detailed studies that give quantitative data about the effectiveness of a given therapeutic agent delivered with a given catheter system. Finally, because there are limits to the animal models used for testing safety and effectiveness of intraventricular delivery methods, the ultimate safety and effectiveness of delivery has to be demonstrated in clinical studies.

CURRENT MYOBLAST CLINICAL STUDIES

There are multiple ongoing or recently completed clinical studies utilizing autologous skeletal myoblasts (Table 2). We describe our current clinical study for the intraventricular catheter injection of myoblasts, which is an extension of the largest series of clinical studies with myoblasts performed in the US. Currently, a randomized study of 24 patients with congestive heart failure (New York Heart Association Classification III-IV) due to previous myocardial infarction is in progress at the Arizona Heart Institute. Patients are randomized 1:1 to undergo percutaneous endomyocardial autologous myoblast transplantation (treatment) and maximal medical therapy, or continue on maximal medical therapy only (control). The cells are injected percutaneously into the endoventricular surface of the previously infarcted left ventricle using 3D mapping and injection system (NOGA, Biosense Webster, Inc., a Johnson & Johnson company, Diamond Bar, CA; and MyoStar, Cordis Corporation, a Johnson & Johnson company, Miami, FL).

Treatment patients are monitored as in-patients during the transplantation procedure and for the first 24 hours. Vital signs and cardiovascular parameters are extensively monitored during the first 24 hours to determine the acute feasibility and safety of the transplantation procedure. The patients are then monitored over a period of 12 months to determine the long-term safety and efficacy of transplants.

TABLE 2. CLINICAL STUDIES UTILIZING AUTOLOGOUS SKELETAL MYOBLASTS		
Trial	**Number of Patients Enrolled**	**Injection Method**
Pagani et al[8]	6	Epicardial, open chest
Menasche[7]	10	Epicardial, open chestt
Siminiak 2004[9]	10	Epicardial, open chest
Siminiak 2005[25]	10	Transvascular
Smits 2003[24] and Ince 2004[23]	5	Endocardial
Dib et al[5]	12	Epicardial, open chest
Dib et al[27]	30	Epicardial, open chest
MAGIC Trial	300 planned, trial cancelled at 100 (+) enrolled	Epicardial, open chest
Herreros 2003[6]	12	Epicardial, open chest

To date, six of the planned 24 patients have been enrolled (three control and three treatment). The transplants have been well tolerated, and the injection procedures have all been successful and without complications. Figure 1A shows the NOGA map from one of the study patients before transplantation, followed by a map of the same patient 3 months after the procedure (Figure 1B). Significant changes are noted that suggest renewed tissue at the site of the implant. We will continue to enroll and test more patients to determine if the findings are consistent with the changes seen in this patient population, and, if results are confirmed, we plan to conduct a phase 2 randomized, double-blind, placebo-controlled study to best test for efficacy of the myoblast transplants. ■

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