Repeat Cell Therapy for Refractory Angina
Déjà vu All Over Again?

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Because the mortality for ischemic heart disease has improved, an increasing number of patients exhaust their revascularization options and are left with refractory angina. Previous studies suggested that up to 15% of patients undergoing catheterization are suboptimal candidates for further revascularization. This number may be growing because a recent analysis from the Duke Databank for Cardiovascular Disease found that 25% of patients had Canadian Cardiovascular Society (CCS) class II-IV angina and coronary disease not amenable to further revascularization. Contemporary data suggest that mortality in these complex patients is decreasing, despite the significant burden of coronary artery disease, whereas rehospitalization rates and resource utilization remain high, reflecting the poor quality of life and functional status in these patients.

Limited treatment options are available for patients with refractory angina beyond pharmacological treatment and revascularization. This unmet clinical need has stimulated the investigation of novel treatment options, including advanced techniques to treat chronic total occlusions, neovascularization, reduction of the coronary sinus, shockwave therapy, and stem cell therapy. Because the primary problem for these patients is inadequate myocardial perfusion, stem cell therapy using angiogenic progenitors represents a theoretically attractive approach. Initial trials for this specific indication have arguably been the most positive in the field of stem cell therapy. Three recent meta-analysis of patients with refractory angina with or without left ventricular dysfunction reach similar and consistent conclusions that this treatment may result in improvements in angina, quality of life, exercise capacity, left ventricular function, and even mortality. Still no definitive Phase 3 trial has been completed, and a large number of questions remain unanswered, including the ideal cell type and method of delivery.

In this issue of Circulation: Cardiovascular Interventions, the group from Leiden builds on their previous work in this area by providing valuable data regarding the benefits of repeat therapy. In 2006, this group first published the results of an open-label trial in 25 patients who were not candidates for revascularization and had CCS III-IV angina, despite optimal medical therapy. The patients were treated with intramyocardial injection of autologous bone marrow mononuclear cells (BMMC) using Noga electromechanical mapping for guidance into ischemic regions. A 3 month follow-up, the cell-treated patients had improvement in CCS angina class, left ventricular function and volumes, as well as myocardial perfusion by single photon emission computed tomography, which was greater in the injected segments versus noninjected segments. This open-label, nonrandomized trial was followed by an important early placebo-controlled trial, which randomized 50 refractory angina (CCS III-IV) patients to intramyocardial injection of 100x10⁶ BMMC versus placebo. Patients treated with BMMC had improvements in CCS angina class, quality of life, left ventricular ejection fraction as assessed by magnetic resonance imaging, and myocardial perfusion compared with placebo-treated patients at 3, 6, and 12 months. A follow-up study at 4 years of the BMMC-treated patients in the randomized trial demonstrated low mortality of 12% (3/25) with only 1 cardiac death, but with some decline in CCS class (3.4±0.5 at baseline, 2.5±0.07 at 6 months, 2.7±0.08 at 12 months, and 3.0±0.08 at 4 years). Finally, the same group published the results of a crossover trial in 16 of the initial 25 placebo-treated patients, which demonstrated consistent improvement in CCS class, quality of life, and myocardial perfusion after BMMC treatment. In summary, over the last decade, the Leiden group had treated a total of 66 CCS class III-IV refractory angina patients with nearly identical protocols using intramyocardial BMMC with Noga guidance.

Mann et al now build on these initial findings with open-label retreatment of a specific patient population: 23 no-option patients who previously responded to therapy in one of the 3 trials, but then subsequently had recurrent angina. Several key findings are worth noting: (1) baseline measures of CCS class, angina, quality of life, and myocardial perfusion of patients entering this study were largely similar to those observed before their initial treatment, suggesting that even in this group of responders, the effect was not durable to 5 years; (2) consistent with observations from registry studies, the number of clinical events, including mortality, in this patient population remained extremely low; and (3) the benefits of repeat administration in this open-label study were similar to what was observed after the initial stem cell injection procedure a mean of 4.6 years earlier.

What are we to make of these observations? First, caution is warranted. The sample size (23 patients) is too small to justify any definitive conclusions, and the possibility of type I errors (false-positive findings) is high, as the authors...
indicate. Furthermore, the nonrandomized nonblinded nature of this follow-up study, although perhaps unavoidable, limits the conclusions which can be drawn in a patient population in which there is a known prominent placebo effect, which may be similar to the improvements observed in this study.

Second, this adds to the growing body of literature (reflected in the meta-analyses noted earlier) that treatment with autologous bone marrow–derived stem cells in refractory angina patients is not only safe but also strongly suggests not only real improvements in angina, quality of life, and myocardial perfusion, but also potentially a lower risk of future cardiovascular events, including rehospitalizations and mortality.

Third, the study draws attention to a void in our understanding of stem cell administration: how long one can expect a benefit (if any) from a single administration, and whether repeat dosing is warranted, indicated, or to be recommended.

Finally, patients with refractory angina seem to be a target population in which progenitor cell therapy may be particularly efficacious. Although discrepant findings have been reported in the use of cell therapy after acute myocardial infarction or in patients with heart failure, the experience in this population is uniformly positive. Although the Leiden experience contains only one double-blind component, multiple other and larger trials performed in a double-blind placebo-controlled manner have consistently demonstrated significant improvements beyond the expected placebo effects.

How does this study fit into the context of cell therapy for refractory angina? In many ways, both positive and negative, its déjà vu all over again.

First, the time for large adequately powered studies has not only arrived, but is overdue. Although initial single-center proof-of-concept studies were vital in establishing the feasibility of regenerative approaches for cardiovascular indications, such as refractory angina, acute myocardial infarction, heart failure, and peripheral arterial disease, for the field to progress and substantive knowledge about the risks and benefits of such therapies to be accrued, large, appropriately powered studies need to be the norm going forward. In this regard, it is especially disappointing that the Efficacy and Safety of Angina (RENEW) trial, which was the first large Phase 3 trial powered to detect substantive benefits of autologous CD34+ cell therapy on exercise capacity, was terminated by the sponsor for financial reasons.

Second, work is needed to better understand this complex patient population, including the epidemiology and clinical outcomes in these patients with limited options. Given the outcomes presented here, it is clear that end points in these trials will need to focus on patient-centered metrics, including parameters, such as functional capacity and quality of life. These end points require rigorous double-blind trials to exclude improvements because of placebo effects.

Third, the work of Mann et al suggest that repeat administration might be helpful with efficacy results that mirror those observed after initial treatment; however, it is important to remember that this is a nonrandomized open-label study using a subjective end point in a group of previous responders who might be particularly likely to respond again. These limitations point to the difficulties posed in evaluating the effectiveness and safety of an invasive therapy with subjective end points.

Finally, resources and interest should be directed to the development of new (including regenerative) therapies for this highly symptomatic patient population with limited treatment options. With regards to regenerative therapy, mounting evidence suggests that treatment of patients with ongoing ischemia with angiogenic cells seems not only theoretically attractive, but also clinically beneficial. The experience of Mann et al once again suggests, but does not prove, that angiogenic cells may be particularly suited and beneficial when used for this indication. It is important for regulatory agencies, investigators, academic leaders, and sponsors to come to consensus on methods and trial designs which would facilitate development of new treatments for this challenging patient population with limited therapeutic options. In this regard, the promising findings of this study are déjà vu all over again and point yet again to the potential for regenerative therapy in this population.

Disclosures
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References


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