Can Endothelial Progenitor Cells Treat Patients With Refractory Angina?

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Rerfractory angina continues to pose a therapeutic challenge for patients and clinicians because treatment options including medication and surgery are limited. Therefore, the idea that cell-based therapy could offer a new therapeutic opportunity continues to raise enthusiasm. With this regard, circulating endothelial progenitor cells (EPCs) have gained significant attention because of their participation in neovascularization and re-endothelialization. EPCs are a specific population of progenitor cells—expressing CD133, CD34, and kinase insert domain receptor, KDR (also known as vascular endothelial growth factor 2, VEGFR-2, and fetal liver kinase 1, FLK1) cell-surface markers—that differentiate into endothelial cells, thereby lining blood vessels and playing a critical role in angiogenesis and vasculogenesis. EPCs incorporate into both new and injured vessels, and release proangiogenic and immunomodulatory factors, making them an ideal candidate for treating patients with ischemic heart diseases like refractory angina.

Although cell-based therapy is exciting, it remains to be established which EPC cell population best targets refractory angina: CD34+ or CD133+ EPCs. Both CD34+ and CD133+ are endogenous cell-surface markers expressed on EPCs that originate from bone marrow and are mobilized into peripheral blood in response to cytokine signaling and injury. During the past decade, it has become possible to purify EPCs by mobilizing them into peripheral blood using granulocyte colony-stimulating factor. Endogenous granulocyte colony-stimulating factor is synthesized by the endothelium, macrophages, and immune cells, and it acts as a cytokine that stimulates bone marrow to produce granulocytes and stem cells and then release them into the bloodstream. Therefore, granulocyte colony-stimulating factor is used pharmacologically to enhance the number of EPCs obtained from patients undergoing cell therapy. Specifically, patients are given granulocyte colony-stimulating factor treatment for 4 to 5 days to mobilize EPCs, which is immediately followed by leukapheresis to separate the mononuclear layer from the peripheral blood. After mobilization and separation, flow cytometry and magnetic sorting are used to purify the population by exploiting the expression of these cell-surface markers. Loss of this cell population is strongly implicated in atherosclerosis and endothelial dysfunction.

Because CD34+ is found both on hematopoietic and EPCs, selection using this epitope results in a heterogeneous population of progenitor cells. CD34+ cells play a role in blocking cell differentiation while enhancing cell proliferation, and also in regulating cell to cell adhesion and cell to bone marrow, lymph nodes, and extracellular matrix adhesion. Although CD34 is an essential marker in identifying hematopoietic and endothelial stem cells, the exact biological function of the CD34 protein family remains elusive. CD34+ cells have demonstrated efficacy in patients with refractory angina. Losordo et al12 showed improvements in exercise tolerance and reductions in angina frequency. Similarly, Wang et al13 showed encouraging results for the intracoronary injection of CD34+ cells in intractable angina—reduction in frequency of angina episodes, increase in exercise time, improvement in Canadian Cardiovascular Society, and significant improvement in myocardial perfusion. CD133+ marks a subpopulation of CD34+ cells and is thought to represent a more robust marker of EPCs. Previous clinical trials have demonstrated encouraging results with CD133+ injections delivered both by intracoronary and transmyocardial routes in patients with ischemic cardiomyopathy. Specifically, Bartunek et al16 demonstrated that intracoronary injection of CD133+ cells enhances cardiac recovery—via increasing left ventricular ejection fraction, myocardial perfusion, and myocardial viability—after myocardial infarction. Likewise, Stamm et al17 showed that intramyocardial delivery of CD133+ during coronary artery bypass grafting is safe and beneficial—improving left ventricular ejection fraction. These promising results evident in ischemic cardiomyopathy prompted Jimenez-Quevado et al18 to investigate the safety and efficacy of CD133+ EPCs in ischemic cardiomyopathy patients with refractory angina who were not candidates for coronary revascularization.

In this issue of Circulation Research, Jimenez-Quevado et al18 present their results from the first study done in man where CD133+ cells were injected transendocardially using the Myostar injection catheter in patients with refractory angina (Figure 1). This was a small (n=28) phase I/II, multicenter, single-blinded, randomized study with the primary end point being safety and the prespecified secondary end point being efficacy measured as the change in myocardial perfusion defect (single photon emission computed tomography) at baseline versus 6 months, 12 months, and 24 months follow-up. The trial successfully demonstrated that transendocardial CD133+ injections are safe in this patient population, consistent with other studies using transendocardial injections19,20 and CD133+ cells. Their initial secondary end point demonstrated no efficacy after cell treatment.
Therefore, Jimininez-Quevado et al addressed other exploratory end points (treadmill test, Canadian Cardiovascular Society class, number of angina episodes/mo, nitroglycerin consumption/mo, and quality of life via Seattle questionnaire) 6 months post CD133+ treatment. In doing so, they suggest that there is evidence of efficacy via an increase in local linear shortening—although these results did not coincide with the results from wall motion index—an improvement in Canadian Cardiovascular Society class, a reduction in angina episodes per month and number of nitroglycerin-table consumption, and an increase in certain questions on the Seattle Angina Questionnaire. Although potentially encouraging, we must remain aware that exploratory end points are hypothesis generating, and require confirmation in other studies.
In vitro, the authors illustrated that these clearly labeled CD133+ cells were angiogenic when cocultured with human umbilical vein endothelial cells, and that after 14 days in culture, the expression of endothelial markers increased. Unfortunately, the authors did not distinguish between human umbilical vein endothelial cells and CD133+ cells in their matrigel assays nor did they show direct evidence for these cells promoting angiogenesis, limiting the ability to conclude that CD133+ cells promote angiogenesis in patients.

Given these preliminary findings, do EPCs hold promise as a future therapy for refractory angina or should other stem cells such as mesenchymal stem cells (MSCs) hold more promise? (Figure 2) Similar to EPCs, MSCs are proangiogenic and anti-inflammatory; however, unlike EPCs, MSCs are immunoprivileged, allowing their allogeneic usage. By virtue of not eliciting an immune response, the use of healthy allogeneic donor cells compared with unhealthy autologous cells is feasible for treating refractory angina. Haack-Sørensen et al showed that intramyocardial MSC injections in patients with refractory angina resulted in a significant increase in exercise capacity via metabolic exercise training, a result that was not shown by Jimenez-Quevado et al using CD133+ cells. More strikingly, they demonstrated a sustained effect 24 months after MSC injection in patients with severe coronary artery disease and refractory angina—increase in exercise time, metabolic exercise training, Canadian Cardiovascular Society class, all parameters of the Seattle Angina Questionnaire and a decrease in weekly number of angina attacks and use of nitroglycerine. Although allogeneic MSCs have not yet been used for refractory angina, our group has demonstrated both efficacy and safety in

Figure 2. Chart illustrating various cell types used in clinical trials for refractory angina. Blue arrows indicate the reported results from cell trials with red wording indicating results reported by Jimenez-Quevado et al. CCS indicates Canadian Cardiovascular Society; EPCs, endothelial progenitor cells; LLS, linear local shortening; LVEF, left ventricular ejection fraction; MET, metabolic exercise training; MSCs, mesenchymal stem cells; and SAQ, Seattle Angina Questionnaire.
patients with ischemic cardiomyopathy. Accordingly, allogeneic MSCs may have a role in refractory angina and therefore can avoid the need to stimulate EPC release in these patients.

Ultimately, the article by Jimenez-Quevado et al in this issue of Circulation Research is an insightful contribution to the limited available literature for the use of CD133+ cells in patients with refractory angina. However, the efficacy results are exploratory and represent a first step compared with that of MSCs and CD34+ cells, suggesting that other cell types should be further explored to identify the selected cells for treating patients with refractory angina truly. This is an important indication for cell therapy and further larger studies are warranted. Specifically, comparison studies should be performed and designed to identify the optimal cell type for use, both from a feasibility and efficacy perspective.

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References

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