The (Translational) Road Less Traveled

Timothy D. Henry, Thomas J. Povsic, Douglas W. Losordo

An anonymous editorial in *Nature Biotechnology* asserted that cell therapy for heart disease has been a failure and should not continue. In actuality, the development of CD34⁺ cells for treatment of refractory angina was a well-informed and well-designed pathway toward Food and Drug Administration (FDA) approval to address an important unmet clinical need. Contrary to what was asserted in the *Nature Biotechnology* editorial, trials of CD34⁺ cell therapy for refractory angina not only met their primary end points but were based on a clear mechanism of action.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

Robert Frost (1874–1963), "The Road Not Taken"

In April 2017, an anonymous editorial was published in *Nature Biotechnology* entitled "A Futile Cycle in Cell Therapy: Should a Cell Therapy for Heart Disease With Scant Evidence of Efficacy Continue to be Tested in Humans?"[1] The authors cite a single, phase 2 study in patients with recent acute myocardial infarction—the PreSERVE-AMI trial—as evidence that "cell therapy for heart disease" has been a failure and that the field should focus more on "bona fide cardiomyocytes or progenitors that may differentiate into heart muscle and defined paracrine factors that may tip the balance from fibrosis toward repair."

We take issue with several points in the editorial, the primary being the anonymous author or authors' apparent disregard of basic principles of therapeutic development, the failure to distinguish between types of heart disease, and a poor understanding of the available evidence in the field, particularly as it relates to the cell type under study.

The test agent in PreSERVE-AMI was the autologous CD34⁺ cell.[2] To date, there have been at least 700 patients enrolled in clinical trials of CD34⁺ cell therapy for ischemic tissue repair. The editors of *Nature Biotechnology* seem to equate the failure of a single, phase 2 clinical trial to show a statistically significant improvement in a clinically ambiguous end point (SPECT [single-photon emission computed tomography] imaging) with a mandate to terminate all therapeutic development efforts for this product, and indeed, more broadly, for all cellular therapeutics near clinical application.

In the world of therapeutic development, it is typical for an agent to be tested in multiple clinical indications to make observations of bioactivity and determine whether an overall clinical benefit is evident in specific settings. In phases 1 and 2, an evaluation of the totality of evidence is mandatory, and exclusive focus on a single end point, outside of the setting of a pivotal phase 3 study, is not appropriate.[3] Furthermore, when discussing the bioactivity of a therapeutic, it is important to review all of the evidence available to make a determination as to whether further study is warranted. Failure to do so would be highly detrimental to medical progress. Termination of clinical development based on a negative imaging end point in 1 study for a single indication would have deprived the medical community of many of its most effective therapeutics. In the case of CD34⁺ cell therapy, the weight of evidence is, in fact, positive, and the clinical development of this therapy for refractory angina is worth reviewing.

Refractory Angina

There is a unique and growing patient population with advanced coronary artery disease no longer amenable to surgical or percutaneous revascularization. These challenging, "no option" patients have significant symptoms despite optimal medical management that severely impair their quality of life and create a large economic burden on society.[4–6] The only therapies for these patients approved in the United States beyond antianginal and secondary prevention medications are enhanced external counterpulsation (which has not been shown to improve exercise time or mortality) and transcutaneous myocardial laser revascularization (which has been shown to increase mortality in this patient population).[4–6] The majority of these patients have preserved left ventricular function, and the source of their problem is myocardial ischemia related to inadequate myocardial perfusion.

CD34⁺ Identification and Preclinical Trials

In 1997, Asahara et al[7] first described a circulating endothelial progenitor cell noting that these CD34⁺ cells were capable of differentiating into an endothelial lineage. Subsequent studies documented endothelial progenitor cells increased vascularization, perfusion, and function in ischemic cardiac and skeletal muscle providing a mechanistic underpinning for use in treatment of ischemic conditions. Purified CD34⁺ cells were more potent than nonpurified cell sources supporting further clinical study of this particular cell type.[8–11]

Refractory Angina Clinical Trials With CD34⁺

Extensive preclinical data in small and large animals provided evidence for safety, demonstrated improvements in

From the Cedars-Sinai Heart Institute, Los Angeles, CA (T.D.H.); Duke Clinical Research Institute, Duke Medicine, Durham, NC (T.J.P.); and Caladrius Biosciences, Inc, Basking Ridge, NJ (D.W.L.).

Correspondence to Timothy D. Henry, MD, Cedars-Sinai Heart Institute, 127 S San Vicente Blvd, A3100, Los Angeles, CA 90048. E-mail timothy.henry@cshs.org

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perfusion, and laid the scientific foundation for progressing to clinical application, notably a phase I/IIa double-blind, randomized, placebo-controlled dose escalation trial in patients with class III/IV angina on optimal medication therapy that began in December 2003.[12] Patients received GCSF (granulocyte colony-stimulating factor) 5 µg/kg per day subcutaneously for 5 days followed by leukopheresis and selection of CD34+ cells. All patients then underwent electromechanical mapping followed by intramyocardial injection of CD34+ cells versus placebo into ischemic areas of myocardium using the NOGA catheter system. The trial demonstrated a reduction in angina from 20.5±11.5 to 9.6±13.3 episodes per week from baseline to 6 months in the cell-treated group compared with 21±16 to 27.0±23.8 episodes per week observed in the placebo group.[12] Nitroglycerin use was decreased, and exercise tolerance was improved in CD34+-treated patients.

A large phase II double-blind placebo-controlled trial, ACT34,[11] using basically identical inclusion/exclusion criteria and cell acquisition/processing procedures, randomized patients to 1 of 2 doses of CD34 cells (1×10^5 or 5×10^5 cells/kg), vs placebo. At follow up, the cell-treated patients showed a significant improvement in the primary end point of angina frequency at both 6 and 12 months (P=0.02) and a significant improvement in exercise time in cell-treated patients 139±151 versus 69±122 s at 6 months (P=0.014) and 140±171 versus 58±146 s at 12 months (P=0.017).[13] For the record, this was the first double-blind, placebo-controlled trial in "no option" patients ever to demonstrate a significant improvement in exercise time!

Based on these positive phase I/IIa and phase II trials, an appropriately powered phase III trial the RENEW study (n=440) was designed under a Special Protocol Assessment negotiated with FDA to achieve approval if the primary end point of the study was met.[14,15] The inclusion/exclusion criteria were basically identical to the double-blind, placebo-controlled phase 2 trial design and included 2:1 randomization to CD34+ (1×10^5 cells per kg) versus placebo with an additional 100 patients in an unblinded standard-of-care arm as mandated by regulatory authorities. The only significant trial design difference was that the cell processing was done at a central location and the cell product was shipped to the trial sites. The trial began enrollment in 2012. Unfortunately, on December 4, 2013, the sponsor halted enrollment not because of safety or efficacy concerns (no data analysis was done before study termination) but for financial reasons. The results of the 112 patients enrolled in the trial demonstrated a consistent and significant improvement in the primary end point of exercise time, as well as consistent benefits for angina and major adverse cardiac events.[15]

Most recently, a patient-level meta-analysis of the phase I, phase II, and phase III trials demonstrated a significant improvement in exercise time, a significant reduction in angina, and a significant reduction in mortality after a single administration of autologous CD34+ cells.[16] These results, encompassing a total sample size similar to what was planned for RENEW, provide strong evidence that intramyocardial CD34+ is an effective therapy for this high-risk patient population with limited options. Furthermore, multiple meta-analyses in trials of "no option" patients with or without left ventricular dysfunction have documented significant improvements in a variety of end points.[17–19]

To summarize the current status of CD34+ cell therapy for refractory angina, preclinical studies in small and large animals have clearly demonstrated improvement in vascularity and myocardial perfusion, and the cell type, CD34+ cells, has been clearly shown to be important for angiogenesis and vascular repair, thereby providing a mechanism of action. Therefore, contrary to the pronouncements of the anonymous editorial, "sound scientific evidence and a well-characterized mechanism of action" have been established, and "much more preclinical work defining a mechanism of action and demonstrating a strong rationale for exposing humans to these procedures" is not needed. Indeed, the primary end points for both the phase II and III trials were met.[13,15]

The mechanism, cell type, and method of delivery were ideal for this specific patient population—a hypothesis that was born out in subsequent double-blind, placebo-controlled phase I, phase II, and phase III trials demonstrating consistent treatment effects on exercise tolerance, angina, and (although not powered for clinical events) a reduction in major adverse cardiac events, including mortality.

Cell Therapy Criticism

Unfortunately, much of the criticism of the field of cell therapy seems uninformed and fails to distinguish between different patient populations, cell types, and methods of delivery. In particular, for the refractory angina patient population with impaired blood flow but typically preserved left ventricular function, the overwhelming focus on "myocardial regeneration" is a distraction because these patients need improved myocardial perfusion, not increased muscle mass. In addition, many of the criticisms leveled at the field, such as the failure to show benefit in well-designed placebo-controlled trials, are unfounded. For example, the IxCell-DCM was a double-blind, placebo-controlled trial, which demonstrated a significant reduction in the primary end point using clinical events (death and cardiac hospitalization) in patients with class 3/4 ischemic heart failure.[20]

In contrast to comments in the recent anonymous editorial,[1] from our perspective, the scientific pathway toward FDA approval of CD34+ cells for refractory angina was indeed "well-informed, disciplined progress toward the generation of data that satisfy the conditions of the regulatory agency." Indeed, the negotiation of a Special Protocol Assessment with the FDA attests to this fact. The weak link in this process was an industry partner that for financial reasons abrogated their responsibility to complete the phase III trial.

In fact, for the patient with refractory angina, CD34+ cell therapy is unique because no other therapy has demonstrated an improvement in exercise time and no other therapy has shown an improvement in mortality heretofore. Perhaps the anonymous editor(s) at *Nature Biotechnology* would do well to more carefully review available evidence before issuing blanket statements or avoid wading into conversations in areas with which they seem to have little familiarity.

Disclosures

T.D. Henry reports that his institution has received research grants from Baxter Healthcare for conduct of the ACT-34 (autologous cell therapy 34) and RENEW studies and was on the Steering Committee for ACT-34 and RENEW. T.J. Povsic reports that his institution has received research grants from Baxter Healthcare for conduct of the ACT-34 and RENEW studies, as well as from Celyad, and reports having received modest consulting fees from Pluristem and Caladrius. D.W. Losordo is employed by Caladrius Biosciences.

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