Harnessing the Potential of Human Autologous Stem Cells to Treat Refractory Angina*

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Refractory angina pectoris is a debilitating clinical condition that has typically been used to describe a subset of patients with chest pain syndrome on maximally tolerated antianginal medical therapy, demonstrable myocardial ischemia, and no coronary revascularization options (1). A multitude of novel treatment options directed at patients with refractory angina, ranging from interventional therapies such as coronary sinus reducer stents to metabolic modulations and therapeutic angiogenesis, are now undergoing more rigorous evaluation (1).

The results of the RENEW (Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina) trial published in this issue of JACC: Cardiovascular Interventions by Povsic et al. (2) are an important milestone toward the possible adoption of autologous human stem cell therapy for the treatment of refractory angina pectoris. It is important to highlight that this effort by the RENEW trial investigators is the culmination of a decade of rigorous investigative work conducted by a select group of ardent proponents of human stem cell therapy. RENEW was a multicenter, double-blind randomized controlled trial evaluating intramuscular (IM) administration of purified autologous CD34+ stem cells in patients with refractory angina with no coronary revascularization options.

The primary efficacy endpoint of this industry-sponsored (Baxter Healthcare, Deerfield, Illinois) pivotal phase III randomized controlled trial powered and designed with regulatory authorities was change from baseline in total exercise time (TET) (2). It was measured using a modified Bruce protocol at 12 months. Key secondary endpoints were: 1) change in angina frequency at 3, 6, and 12 months; and 2) change in TET at 3 and 6 months; the key safety endpoint was the incidence of major adverse cardiovascular events through 24 months.

Because of premature sponsor termination of the study for strategic reasons, independent of any unblinded analysis, only 112 of the planned 444 patients were enrolled. RENEW was therefore an incomplete experiment underpowered to assess its primary efficacy endpoint. Despite this limitation, patients treated with stem cell therapy displayed better exercise capacity at each time point, longer mean and median TET at 6 months, and numerically fewer angina episodes at 3 and 6 months. There was no safety signal from the trial for major adverse cardiovascular events, cardiac perforation, or ventricular arrhythmia. Although these findings are in line with previously published studies in this area, the magnitude of benefit in the placebo arm of this study was unprecedented (3). There was consistent improvement in TET and an impressive 90% reduction in angina frequency with placebo. The investigators...
attribute this to rigorous blinding procedures, difficulty with documentation of angina episodes, and knowledge of premature trial termination. However, this reinvigorates the debate on whether “soft” and highly variable endpoints such as TET and angina frequency, affected by myriad uncontrolled factors even in the setting of a randomized controlled trial, are best suited to capture the efficacy of cardiovascular stem cell therapy (4). Although these tests are functional and have been frequently used in trials of new pharmacological or device therapies for angina pectoris and peripheral artery disease, they are prone to considerable patient and testing variability as well as marked placebo response. In a publication reviewing treadmill testing in clinical trials, 92% of sites had problems with their treadmill equipment, 58% did not perform proper treadmill familiarization, and 24% did not start or end the treadmill tests appropriately (5).

The variability and problems with angina reporting despite rigorous pre-screening of participants are highlighted by this trial. Missing and retroactive filing of symptom diaries by patients in clinical and study settings are well known (6). Although both TET and angina frequency have traditionally been accepted for regulatory treatment indication studies in cardiovascular medicine, the limitation of these endpoints has been emphasized by the RENEW trial. Improvement in health-related quality of life is highly meaningful to patients with chronic ischemic heart disease, and the providers who treat these patients, and may be better suited as an endpoint for clinical research in this area (7).

Given the limited understanding of the mechanistic aspects of CD34+ mononuclear cell therapy for refractory angina, the absence of myocardial perfusion imaging as a surrogate or exploratory endpoint is clearly a missed opportunity. Although at an additional cost, demonstration of a clear-cut mechanism to explain the observed functional benefit of this treatment surely would help it gain acceptance in the community. The challenge, of course, is to define an imaging modality that is readily available and feasible in a multisite clinical trial setting. It must also be able to detect subtle changes in myocardial blood flow related to angiogenesis that results in improved collateral vessel formation, transmural flow gradients, and subendocardial perfusion (8). A nested cohort to assess cardiac blood flow with magnetic resonance imaging while assessing the functional effects of therapeutic angiogenesis may be feasible.

In the RENEW trial, an independent review of coronary angiograms was performed to ascertain that the eligible patients had no epicardial revascularization options. Information in the published report regarding the criteria by which patients were deemed unsuitable for revascularization is missing and would be very instructive. Undoubtedly, the scope of contemporary percutaneous coronary intervention has improved significantly with advanced coronary bifurcation and chronic total occlusion intervention techniques. Also, selection of such patients with severe manifestation of coronary artery disease that precludes percutaneous coronary intervention or coronary artery bypass graft surgery may represent those with failure of their own natural angiogenic response and/or resistance to various neovascularization stimuli (9). In addition, commonly used medications, including aspirin, prescribed to patients with chronic ischemic heart disease have angiogenic-inhibitory effects, and this area is not well addressed in the final study results (10).

The question of optimal dosing and delivery of stem cells remains unresolved. The RENEW investigators chose the delivery of bone marrow subpopulation of CD34+ endothelial progenitor cells using an IM route into ischemic myocardium with NOGA mapping (Biologics Delivery Systems, Irwindale, California). This combination is invasive but has shown promise and an acceptable risk profile in prior studies. The safety and feasibility of this approach were reaffirmed in this study, but the questions of dose and timing of clinical effects remain largely unresolved. IM delivery of stem cells requires highly specialized equipment and expertise and is associated with finite risk for myocardial perforation. The centralized isolation of CD34+ cells from mobilized peripheral cell product using a Baxter Healthcare ISOLEX 300i system is highly innovative and demonstrates the feasibility of this treatment approach in clinical practice. It also allowed thorough blinding of the injected cells. Thus, the RENEW trial design highlights the assessment of objective and subjective endpoints using a well-designed and rigorously blinded procurement and administration of stem cells to patients with refractory angina pectoris. The IM protocol included 10 × 0.2 ml injections of 1 × 10^5 to 1 × 10^7 CD34+ cells/kg or placebo. On the basis of prior pre-clinical and clinical experience, 1 × 10^5 cells/kg is considered low dose and 5 × 10^5 cells/kg a high dose (2). Thus, the RENEW trial tested a broad range of CD34+ cells from low to very high dose. The relationship of stem cell dose to effect has not been linear, and in the ACT34 (Adult Autologous CD34+ Stem Cells) clinical trial, the low-dose CD34+ cells demonstrated a more profound improvement in exercise tolerance compared with high dose (5 × 10^5 cells/kg) at
6 and 12 months (3). This benefit with low-dose CD34+ cell IM injection is attributed to a paracrine effect. On the basis of these findings, the selection of a broad CD34+ cell dose range may potentially limit the therapeutic efficacy in the RENEW trial. The more recently published 2-year results of the ACT34 trial demonstrated that patients treated with both low- and high-dose CD34+ cells had a significant reduction in angina frequency, and longer term evaluation of myocardial angiogenesis studies may be warranted (11). The 24-month major adverse cardiovascular event evaluation in the RENEW trial is therefore justified. Nevertheless, the topic of optimal dosing remains controversial and has not been definitively settled.

Treatment of patients with advanced ischemic heart disease and refractory angina pectoris is challenging, often unrewarding both for patients and providers, and associated with significant cost in terms of health care delivery and loss of socioeconomic productivity (1). Hence, innovative strategies to address this clinical problem are and will remain highly relevant. However, substantial improvements in quality of life and angina control along with a demonstrable mechanism would be necessary to justify the expensive and potentially invasive therapy of IM delivery of autologous stem cells. It would be appropriate to conclude that the incomplete RENEW trial experience is only a feasibility demonstration of this approach. Nevertheless, it moves the field forward, for which the RENEW investigating team deserves credit.

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