Editorial

Mesenchymal stromal cells and ischemic heart disease: hitting the target?

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A recent study by researchers from the Copenhagen University Hospital assessed the impact of marrow-derived mesenchymal stromal cell (MSC) administration in human patients with ischemic heart failure. Outcomes from this randomized, double-blind, placebo controlled trial, which were reported in *the European Heart Journal* in July of 2015 (1) indicate that intra-myocardial stem cell delivery is well-tolerated and yields measurable improvements in myocardial function. In this study patients receiving MSCs (n=40) or placebo (n=20) exhibited similar baseline characteristics before treatment, and their cardiac function was evaluated at 6 months post-treatment by magnetic resonance imaging (MRI) or computed tomography (CT). Importantly, the study achieved its primary endpoint of efficacy, which was a significant reduction in left ventricular end-systolic volume (LVESV) in the MSC treatment group (–7.6±13.2 mL; P=0.001). In contrast, the placebo treatment group showed no significant change in LVESV (5.4±12.5 mL; P=0.07) while the difference between treatment groups was also highly significant (P=0.001). MSC administration also yielded significant improvements in left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), systolic volume (SV), and cardiac output (CO) at 6 months post-treatment. None of these parameters were significantly altered in patients receiving placebo, and all but LVEDV differed significantly between treatment groups. MSC administration also resulted in a significant increase in left ventricular (LV) mass, end-systolic wall thickness, and reduced scar mass.

An interesting caveat to the study was that patients received autologous MSCs at a dose $(77.5\pm67.9)\times10^6$ that was determined by the total cell number recovered after culture expansion for two passages. Although actual doses were not reported for individual patients, the authors segregated patients into three separate groups (<43 Mil, 43–83 Mil, >83 Mil) based on total cell dose to evaluate dose-dependent effects on outcome. This analyses revealed a significant (P=0.045) difference in LVESV between patients administered the high (>83 Mil) *vs*. low (<43 Mil) cell dose. Furthermore, changes in LVEF and mean myocardial mass exhibited a clear trend of dose dependency but differences between doses did not reach statistical significance. The study also reported significant improvement in prognostic markers including the New York Heart Association (NHYA) functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, as well as in the 6-minute walk test for both treatment groups at 6 months post-treatment *vs*. baseline, but differences between treatment groups were not significant. The authors argue that this result reflects a strong placebo effect.

Overall, results from this study suggest the suitability of autologous, bone marrow-derived MSC administration as a possible treatment strategy for chronic myocardial ischemia. Moreover, this study differs significantly from other MSC-based cardiology trails in several respects. First, most trails completed to date have evaluated the efficacy

of bone marrow mononuclear cells (BMMNCs) or MSCs administered to patient's after acute myocardial infarction (2-11). Second, a number of such trails have failed to meet their primary endpoints of efficacy (4,9,10,12,13), which this study did achieve. Third, most trials have failed to demonstrate any effect of cell dose on outcome, and one trail conducted in patients with ischemic cardiomyopathy (POSEIDON) demonstrated an inverse dose response of MSCs in reducing scar size (4). The present trial did detect a significant difference in end-SV as a function of MSC dose even though it was not specifically powered to discriminate dose-dependent effects on outcome.

Despite the promising results of the present study, which evaluated patients with no additional treatments other than MSC infusion, overall outcomes of cell-based therapies for heart disease have yielded mixed results. For example, a meta-analysis of outcome data for acute myocardial infarction or ischemic cardiomyopathy patients infused with BMMNCs reported a modest but significant improvement in LVEF, LVESV, LVEDV and infarct scar size (14), while meta-analysis of trails involving only AMI patients failed to demonstrate any clinical benefit of BMMNC infusion on LV parameters, major adverse cardiac events, or life-expectancy (15). A separate meta-analysis of AMI patients did find a significant effect of BMMNCs on LVEF, LVESV and infarct size but subgroup analysis of studies that employed MRI-derived endpoints failed to detect a significant effect on cardiac function, cardiac volumes, or infarct size (16). Importantly, a trend toward improvement in cardiac function in patients treated with MSCs was evident. A major pitfall in meta-analysis studies including those discussed above is the introduction of bias related to inclusion of clinically heterogeneous cohorts. Moreover, the aforementioned studies pooled data from trials that employed BMMNCs, CD34+ and CD133+ cells, cardiosphere-derived cells, and in some cases MSCs. Furthermore, they did not compensate for differences in culture methods and duration, and the quality of each cellular product with respect to potency is rarely evaluated empirically. Consequently, it is impossible to determine if patients enrolled in different trials or given autologous cells in a single trial are administered a therapeutic of consistent cellular composition and potency, and more importantly, if potency is appropriately matched with the given disease indication. The inability to quantify cell potency prior to patient administration represents a major impediment toward development of more efficacious MSC-based therapies.

To begin to address this issue, our group recently developed a clinical indications predictions (CLIP) scale to assess MSC potency prior to patient administration (17). Specifically, we demonstrated that intrinsic differences in cell growth and colony forming unit-fibroblast (CFU-F) activity of different human MSC isolates were correlated with *TWIST1* expression levels, and that *TWIST1* levels also predicted differences in angiogenic, anti-inflammatory, and immunomodulatory activity as well as multi-potency in cell-based assays and *in vivo*. Importantly, these findings revealed that intrinsic differences in growth rates of different MSC isolates reflected functional differences in biological activity and therapeutic potency. Consequently, selecting for highly proliferative populations, which is often done to meet the target cell dose, may enrich for subpopulations of cells that are non-efficacious or contraindicated for a given disease indication. Use of the CLIP scale will aide in prospectively matching MSC isolates to specific patient populations prior to treatment thereby resulting in more predictable and beneficial outcomes. Naturally, other metrics in addition to the CLIP scale are needed to encompass all possible clinical applications of MSC-based therapies. Recently, the International Society of Cellular Therapy (ISCT) proposed a matrix-based approach employing gene and protein expression data coupled with functional-based assays with immune responder cells to evaluate the immunomodulatory activity of MSC products used in clinical trials targeting immune-related disorders (18). Other groups have also described potency assays to assess immunomodulatory activity (19) and osteogenic potential (20) of human MSC isolates. Collectively, these studies serve as a blueprint for further assay development, and their use to pre-screen populations prior to patient administration is anticipated to enhance overall clinical efficacy in future trials.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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patients with severe ischaemic heart failure: a randomized placebo-controlled trial (MSC-HF trial). Eur Heart J 2015;36:1744-53.
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