Adipose-Derived Mesenchymal Stem Cell Therapy for Ischemic Heart Disease: Safe but Not Effective?

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Short Editorial related to the article: Safety and Efficacy of Adipose-Derived Mesenchymal Stem Cell Therapy for Ischemic Heart Disease: A Systematic Review

Cardiovascular disease continues to be the leading cause of death in adults globally.[1] Obstructive coronary artery disease involves a gradual narrowing of coronary artery branches due to the build-up of atherosclerotic plaque, leading to reduced blood flow to the myocardium.[2] This myocardial infarction initiates a cascade of pathological processes such as oxidative stress, inflammation, and fibrosis, which eventually lead to heart failure. A heart transplant is sometimes the only viable option for many patients with progressive ischemic heart failure refractory to anti-anginal medication or revascularization.[3] Novel therapeutics such as stem cells, RNAs, CRISPR, growth factors, etc., hold great promise for meeting this clinical need. Stem cells have been tested in pre-clinical studies extensively for many years now. Paracrine factors, instead of differentiation potential, are now widely agreed upon as the most likely cause of their therapeutic effects. Contemporary studies continue to employ either native or genetically reprogrammed stem cells for treating various diseases. Stem cells can be derived from diverse niches in the adult human body, such as blood, bone marrow, fat, skeletal muscle, and more.[4] However, many of these tissues can only be harvested in very small quantities. Also, access to some of them, e.g., bone marrow, requires invasive procedures. Adipose remains one of the most abundant and easily retrievable tissues for this purpose.[5]

In the current issue, the authors[6] present a systematic review of clinical studies in which adipose-derived stem cells (ADSCs) have been used as a therapeutic for ischemic heart disease (IHD). This review summarizes the safety and efficacy of ADSCs in ten such studies (comprising 29 publications), with 8 randomized controlled clinical trials and 2 uncontrolled trials. The studies reviewed by the authors administered varying numbers of ADSCs (from 400,000 cells in the Athena I trial[7] to 100 million cells in the DANISH[8] and SCIENCE[9] studies. Apart from the AdiFLAP[10] study, which used an adipose patch, these studies administered ADSCs via intramyocardial or intracoronary injections. Follow-up for these trials ranged from 6 months (APOLLO,[11] Kastrup et al.[12]) to 36 months (MyStromalCell[13] and PRECISE[14]). In the early days of stem cell therapy, one of the main safety concerns was teratoma formation.[15] This was largely due to the pluripotent nature of stem cells being tested. As the human body is a complex milieu of growth factors, cytokines, hormones, etc., stem cells could also differentiate into unintended cell types, making stem cell therapy a risky endeavor that could cause more harm than good. In the last decade, these therapies have come of age, with multipotent instead of pluripotent stem cells as candidates.

With regard to safety, only a few adverse sequelae, such as transient ischemic attacks and hospitalization due to worsening angina, were reported in the studies reviewed. Taken in context, it is likely that these events occurred due to underlying cardiovascular disease. In this aspect, ADSCs are comparable to other stem cell candidates for the treatment of IHD.[16]

However, the efficacy of ADSC therapy is a mixed bag. None of the studies reported a significant improvement in cardiac function between the control and experimental groups. However, three studies showed a reduction in stress-induced ischemia in the treatment groups by myocardial perfusion scintigraphy.[11] This observation is promising, as increased blood flow is physiologically coupled to improved contractility of the heart muscle. This is reflected in one study where myocardial segments treated with ADSCs exhibited improved parietal motility vs control.[11] Follow-up measurements in various studies showed improvements in other endpoints, such as the six-minute walk test or increase in systolic volume. The two most recent studies, DANISH[8] and SCIENCE[9] did not report any improvements in the experimental group for their primary and secondary endpoints. Although rapid enhancements would have been ideal, the effects of ADSC treatment did improve the quality of life in these patients in the long term. These results must be interpreted in light of the heavy burden of disease carried by recipients of ADSC therapy. The timing of ADSC treatment likely played a crucial role in the modest improvements in the subjects. In the studies reviewed by the authors, ADSCs were administered to patients in the late stages of IHD.[6] Earlier ADSC treatment could potentially rescue cardiac function and minimize infarct size in the future. As developments in stem cell delivery techniques continue, phase III clinical

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studies with more subjects and longer follow-up periods will reveal the full potential of ADSCs. This systematic review synthesizes pertinent clinical data and serves as a useful resource for the development of ADSC therapy.

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