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Endogenous Laser Induced Ventricular Enhancement (ELIVE™) Therapy: A New Paradigm for Treating Heart Failure?

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Abstract

Endogenous Laser Induced Ventricular Enhancement (ELIVE™) therapy is an innovative approach of treating heart failure, evolved from the results achieved in a clinical trial that assessed safety and feasibility of laser-supported $CD133^{pos}$ intramyocardial cell transplantation in patients suffering from ischemic cardiomyopathy. This study demonstrated significant restoration potential of hibernating myocardium upon autologous, bone marrow-derived cell transplantation when supported by low-energy laser treatment. ELIVE™ therapy now employs a new generation of laser, featuring a hollow fiber waveguide, rendering this approach amenable for a minimally invasive procedure, in combination with a preceding granulocyte colony stimulating factor (GCSF) treatment of the patient in order to mobilize endogenous stem and progenitor cells. The rationale of this new therapy is for the patient himself to become his own 'bioreactor', effectively triggering and amplifying endogenous regeneration mechanisms based on autologous stem and progenitor cells.

Keywords: Cell therapy; Laser therapy; Ischemic cardiomyopathy; Hibernating myocardium; Magnetic resonance imaging

Endogenous Laser Induced Ventricular Enhancement (ELIVE™) Therapy

More than a decade ago first trials for bone marrow stem cell therapy in cardiac patients commenced [1], hoping the transplantation of such autologous stem cells would lead to new ways in treating heart failure. Since then, a large number of different cell therapy studies have been reported, with various results [2], most of which resulting in only marginal improvements.

A multicenter clinical phase I trial in which patients with severe ischemic cardiomyopathy underwent coronary artery bypass grafting (CABG) with subsequent transepicardial laser treatment and autologous $CD133^{pos}$ cell transplantation, showed remarkable improvement in cardiac function [3-5], significantly exceeding outcomes from other cell transplantation studies. While CABG, laser therapy, and cell transplantation must be assumed to have contributed to these results in a combined manner, other publications have shown a benefit of autologous cell transplantation without bypass surgery [6], and the combination of cell and laser therapy was not only shown to be effective [7,8], but analyses of the aforementioned clinical trial demonstrated laser treatment to be essential to further support the benefit of cell transplantation by initiating a re-remodeling process of the heart. Magnetic resonance imaging (MRI) analysis prior and post treatment determined a correlation between the amount of hibernating myocardium in the ischemic heart and the clinical outcome, explaining the significant increase in left ventricular ejection fraction (LVEF). Delayed enhancement MRI, a utility in myocardial assessment [9], showed that an extended area of transmural delayed enhancement (>3 myocardial segments), as assessed preoperatively, was inversely correlated with an LVEF increase after laser-supported cell therapy. Furthermore, marker analyses subsequent to laser treatment resulted in an increase of $c\text{-}kit^{pos}$ cells, suggesting resident cardiac stem cells (eCSCs) are directly and positively affected by laser therapy, improving endogenous regeneration. Since eCSCs restore cardiac function by regenerating lost cardiomyocytes [10], myocardial damage and heart failure may spontaneously reverse anatomically and functionally upon eCSC activation through laser treatment.

ELIVE™ therapy utilizes this effect of endogenous regeneration potential. To date, the most suitable cell type to be used as a transplant to treat heart failure is not known. Various cell types from various sources keep being considered, and more recently efforts have been made to bioengineer stem cell types specifically for cardiac regeneration [11]. While these works are important, and necessary, to evaluate the capacity of stem cell therapy, any approach of transplantation cell therapy has to overcome considerable regulatory obstacles. Also, there is reason to believe that laser treatment in combination with cell therapy will boost any transplanted cell type's therapeutic potential, so that in addition to the work of Masumoto et al. we propose not only to evaluate injectable biomaterials, but also other means to potentially trigger endogenous repair mechanisms. As our studies suggest such endogenous mechanisms to be in place, and effective when triggered and amplified, ELIVE™ therapy opts to replace cell transplantation by a preceding GCSF treatment to initiate mobilization of the patient's own stem and progenitor cells [12,13] without ever leaving the body, and to further support proliferation. The laser serves to stimulate endogenous regeneration mechanisms and triggers the homing effect for any

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mobilized cells, to recruit eCSCs, and thus to amplify the endogenous re-remodeling potential of the organ.

The advantages of such an approach are obvious: since a mode of action of any given cell transplant is not well understood, ELIVE™ therapy utilizes the potential of all autologous stem and progenitor cells that are mobilized, or recruited. As the patient is serving as his own bioreactor, this approach of cell therapy obviates the requirement for any additional cell transplantation or biologic injection, renders good manufacturing practices (GMP) requirements unnecessary, and avoids any regulatory issues. ELIVE™ is the only application known to trigger a re-remodeling of the heart; it attacks more systemically progressing heart failure rather than being limited to a symptomatic treatment only. As such, it is typically indicated to treat Class III and IV heart failure patients. However, since indications include any deficiency in heart function provoking the initiation of remodeling in the organ, an early indication is suggested, so to treat already during the onset of heart failure rather than after manifestation, and thus to possibly include Class II patients as well.

The ELIVE™ laser, featuring a hollow fiber waveguide beam delivery device, renders this approach amenable for an endoscopic procedure, which will enable endocardial application in the cath lab where most cardiac procedures are performed. The minimally invasive approach also provides the option of repeatable treatment as the underlying cause for heart failure might progress over time.

ELIVE™ therapy, a combination of laser-supported endogenous cell therapy is expected to create a paradigm shift in how to treat heart failure. It suggests endogenous regeneration processes to be in place, and sufficient, to effectively improve cardiac function, based on the potential of endogenous cells when sufficiently mobilized, supported by the laser-induced amplification of intrinsic repair mechanisms of the organ, and the provision of a homing effect for such cells.

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