Novel Ideas for the Treatment of No-Option Critical Limb Ischemia

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ABSTRACT

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Mini Review

Critical limb ischemia (CLI) is the advanced stage of peripheral arterial occlusive disease (PAOD). This stage can be considered as a step prior to impending gangrene and amputation. Recently, it has been demonstrated that the use of stem cells and gene therapy, either alone or in combination in cases of no-option CLI, can provide therapeutic benefits in terms of relieving the rest-pain and healing the ischaemic ulcers. It seems, that although such combinations of treatment are safe, a grey area still exists to whether they are effective in reducing the risk of amputation and improving the quality of life to a reasonable degree. More studies are necessary.

Considerations

Critical limb ischemia is characterized by severe obstruction of the arteries, reduction of blood flow to the extremities, rest pain and tissue loss. A step farther stands the no-option CLI, where neither the use of vasoactive drugs nor the use of open or endovascular procedures respond well. This implies that a significant percentage of such patients will have a below or above knee amputation in the foreseeable future. For such patients, only some "exotic" interventional and some new non-interventional remedies exist, which are based on angiogenesis [1-5]. It has been demonstrated that the use of stem cells alone or in combination with gene therapy can provide therapeutic benefits in terms of relieving rest-pain and healing the ischemic ulcers. Main steps when using stem cells are:

- a) Harvesting
- b) Separation
- c) Activation
- d) Administration of stem cells to the patient.

The use of stem cells for angiogenesis is based on the principles of holistic medicine. Various studies have shown that cellular mediators and tissue-specific chemokines may facilitate selective recruitment of bone marrow stem and progenitor cells [5-8], improving blood flow in the limbs, retina and the myocardium, via angiogenesis. Consequently, the principle for therapeutic application of stem cells in CLI, is aiming to the restoration of vascular cellularity and control of the newly formed vessels. End results are characterized by less pain, better healing of ulcerations and improved sitting, standing and walking (Figure 1). Angiogenesis can be considered as the transformation of nonfunctional collateral arterioles into functional. Evidence showed that stem cells deriving from human bone marrow can promote arteriogenesis. Two major factors were used to mobilize these stem cells:

- a. Granulocyte colony stimulating factor (G-CSF)
- b. Granulocyte-macrophage colony-stimulating factor (GM-CSF).

Figure 1: The aim of the procedure is to activate the non-active mesenchymal stem cells and replace the damaged cells with activated identical new cells.

Therapeutic administration of stem cells does not imply that their origin is from bone marrow only, but also from adipose tissues and umbilical cord. Nevertheless, injection of bone marrow mononuclear cells (BM-MNCs) has significantly improved pain-free walking time, rest pain and tissue oxygen pressure 6 months after treatment in no-option CLI patients, whereas injection of mononuclear cells from the peripheral blood, did not lead to similar effect. These findings suggested that angiogenic-cell-therapy is a valid choice and is not inferior to the conventional revascularization therapies in patients with no-option CLI. Stem cells have been used for therapeutic purposes the last 40 years [9-11]. For example, bone marrow transplantation is a life-saving procedure for patients with certain types of bone marrow diseases and malignancies. In the past, the usefulness of stem-cell-transplantation, was limited by the fact that some organs (like brain, spinal cord, heart, and kidney) were thought to lack detectable stem cells. Several recent discoveries have revolutionized stem cell biology. What are these discoveries?

- (a) Stem-cells have been detected in organs, such as brain and muscles that were thought to lack regenerative potential.
- (b) Similarly, it has been shown that skeletal muscle stem cells (myoblasts) can be cultured *in vitro* and then transplanted into a recipient's muscle, where they can re-populate the damaged muscle.
- (c) Specific stem cells appeared to display much more plasticity than originally thought. This implies, that isolated stem-cells from one tissue can differentiate into a variety of nonrelated cell-types and tissues.
- (d) It has been demonstrated that under appropriate culture conditions, embryonic stem cells have the capacity for replication *in vitro*.

- (e) Recently, "hypoxia inducing factors" have been shown to activate specific pathways, that may control stem-cell self-renewal. These factors may prove to be of therapeutic value since many cancers were considered to be developed from "self-renewing cancer stem cells". All these observations have expanded therapeutic utility of cell-based treatments.

Furthermore, stem-cell therapies, in combination with gene therapies, may prove to be useful in the treatment of a variety of human diseases. In particular, certain vascular groups of patients with very poor outflow and other comorbidities, cannot be subjected to any revascularization procedure. Similarly, patients who had several failed revascularization attempts, cannot be considered as good candidates for a new open or endovascular surgical procedure [11-13]. These subgroups of patients, represent a population with the highest rate of limb loss and death. In such patients, angiogenesis through the administration of stem cells alone or in combination with new gene therapies, may become a standard strategy. Gene therapies involve a vast new field for treating inherited and acquired diseases. This kind of therapy implies the genetic modification of cells to produce a therapeutic effect (Figure 2). Such genetic modification can be carried out either in cultured cells *in vitro*, which then are administered to the patient, or may involve modification of cells, *in vivo*. Most approaches to gene therapy involve 3 interacting components:

- a) The presence of a therapeutic gene
- b) A vector that allows delivery of the gene to the appropriate cell, and
- c) A device (i.e. a catheter or stent) for delivering the gene/vector complex to the appropriate tissue *in vivo*.

Figure 2: Exploring the possibility to improve blood flow using genes.

(Figure 3). Finally, combined clinical trials of stem and gene therapy have demonstrated that vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) can be delivered as proteins or DNA. The results still are under consideration, because some gray areas appeared (i.e., insufficient duration of the exposure of the ischemic tissue to the growth factors in order to promote the production of stable vessels) [14,15]. The development of more efficient gene transfer systems will probably make these novel therapies more effective in improving the symptoms of CLI. Future plans for using such therapies

- a) Combination of stem cells and gene therapy in no-option CLI.
- b) Combination of embryonic stem-cell and gene therapy in ischaemic heart disease
- c) Combination of stem cells and gene therapy in chronic ischaemic colitis.
- d) Prevention of acute mesenteric ischemia, by using combinations of stem-cell and gene therapy.

Figure 3: Principle of gene therapy, in general.

We have to keep in mind, that gene and stem-cell therapies raise a number of important ethical issues and concerns. Some of them, are common to any new therapy involving human experimentation. Others are more unique to specific methods used in gene and stem cell therapeutics. Nevertheless, such ethical debates will continue to be an important determinant of the progress of similar therapies in the future.

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