Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Review

Cell therapy of critical limb ischemia in diabetic patients – State of art

Michal Dubský [a,*], *Alexandra Jirkovská* [a], *Robert Bem* [a], *Andrea Nemcová* [a], *Vladimira Fejfarová* [a], *Edward B. Jude* [b]

[a] *Institute for Clinical and Experimental Medicine, Prague, Czech Republic*
[b] *Diabetes Centre, Tameside Hospital NHS Foundation Trust and University of Manchester, Lancashire, UK*

ARTICLE INFO

Article history:
Received 30 September 2016
Received in revised form
19 December 2016
Accepted 22 February 2017
Available online 27 February 2017

Keywords:
Critical limb ischemia
Cell therapy
Diabetes mellitus

ABSTRACT

In this review we report on the state of cell therapy of critical limb ischemia (CLI) with respect to differences between diabetic and non-diabetic patients mainly from the clinical point of view. CLI is the most severe form of peripheral arterial disease and its diagnosis and treatment in diabetic patients is very difficult. The therapeutic effect of standard methods of CLI treatment is only partial – more than one third of diabetic patients are not eligible for standard revascularization; therefore, new therapeutic techniques such as cell therapy have been studied in clinical trials. Presence of CLI in patients with diabetic foot disease is associated with worse clinical outcomes such as lack of healing of foot ulcers, major amputations and premature mortality. A revascularization procedure cannot be successful as the only method in contrast to patients without diabetes, but it must always be part of a complex therapy focused not only on ischemia, but also on treatment of infection, off-loading, metabolic control of diabetes and nutrition, local therapy, etc. Therefore, the main criteria for cell therapy may vary in diabetic patients and non-diabetic persons and results of this treatment method should always be assessed in the context of ensuring comprehensive therapy.

This review carries out an analysis of the source of precursor cells, route of administration and brings a brief report of published data with respect to diabetic and non-diabetic patients and our experience with autologous cell therapy of diabetic patients with CLI. Analysis of the studies in terms of diabetes is difficult, because in most of them subanalysis for diabetic patients is not performed separately. The other problem is that it is not clear if diabetic patients received adequate complex treatment for their foot ulcers which can strongly affect the rate of major amputation as an outcome of CLI treatment.

* Corresponding author at: Videnska 1958/9, 14021 Prague 4, Czech Republic. Fax: +420 261362820.
E-mail address: michal.dubsky@gmail.com (M. Dubský).

http://dx.doi.org/10.1016/j.diabres.2017.02.028
0168-8227/

Contents

1. Introduction

Peripheral arterial disease (PAD) defined as vascular occlusion below the level of inguinal ligament is one of the most severe complications of diabetes and increases the risk for failure to heal the ulcer and lower-limb loss [1]. In accordance with International Working Group on the Diabetic Foot (IWGDF) Guidance the diagnosis of PAD is often challenging due to lack of typical symptoms such as claudication or rest pain. Standard diagnostic methods for PAD can be affected in patients with diabetes by the presence of peripheral neuropathy, infection, oedema and calcifications in arterial walls [1,2].

PAD is strongly prevalent in patients with diabetes, more than 50% of patients with diabetic foot ulcer (DFU) have coexisting PAD [3]. Many factors lead to decreased angiogenesis, progression of inflammation and endothelial dysfunction and therefore to acceleration of PAD in diabetes [4–6]. Angiogenesis may be impaired in patients with diabetes due to the hyperglycemia which can reduce the hypoxia-dependent protection of hypoxia inducible factor-1 alpha (HIF-1α) against proteasomal degradation [7]. Moreover, the increased plasma nitric oxide inhibits angiogenesis and can decrease the levels of several pro-angiogenic growth factors. Recruitment of endotelial precursors cells (EPC) which are stimulated by stromal-derived factor alpha (SDF-1α) and expressed by epithelial cells and myofibroblast and the activation of endothelial nitric oxide synthase are both involved in reduced EPC mobilisation in diabetic patients Moreover, hyperglycemia inhibits hypoxia induced VEGF expression by decrease of activation of HIF-1α which can also lead to impaired angiogenesis [8].

The prognosis of the most severe form of PAD; critical limb ischemia (CLI) without the possibility of revascularization is very poor. These patients have a 40% risk of major amputation and 20% risk of mortality [9]. Up to one third of patients with PAD are not suitable for revascularization by percutaneous transluminal angioplasty (PTA) or bypass due to excessive operative risk or unfavorable vascular involvement and could achieve therapeutic benefit from autologous stem cell therapy as an adjunctive technique in the management of PAD [10]. Faglia et al., reported the clear trend toward the first choice of PTA over by-pass surgery, but there has been no head to head randomized trials in diabetic patients [1,11]. The technical failure of PTA in patients with diabetes is around 10%. These standard revascularization procedures are often not eligible in patients with severe CLI especially long-segment occlusions and distal disease which is characteristic for diabetic patients [12]. Spanos reported good long term outcomes of hybrid procedures in the treatment of multi-segmental chronic PAD, whereas diabetes remained the determinant factor for worse outcome of these procedures [13]. Therefore new therapeutic techniques, such as gene or cell therapy for these “no-option“ patients have been researched - in contrary with cell therapy, meta-analysis of randomized clinical trials of gene therapy by vascular endothelial growth factor (VEGF) showed no significant differences between placebo and active groups for any outcomes [14]. On the other hand, there are several metaanalyses that summarized the efficacy of cell therapy in the treatment of CLI and prevention of major amputation both in diabetic patients and non-diabetic individuals [10,15–17].

2. What type and source of precursor cells?

Some sources of precursor cells are controversial either from physiological mechanism of action or ethical consequences. There have been no reports about the usage of embryonic stem cells in the treatment of CLI; this type of treatment has many ethical concerns and in most European countries is not approved by regulatory authorities. There has been one phase I study of human cord-blood derived mesenchymal stem cell (MSC) therapy of CLI from South Korea which concluded that this type of cell treatment is safe and well tolerated [18]. Adult stem cell therapy depends on the origin of separated cells – xenogeneic, allogeneic or autologous. The use of xenogenic cells is still not approved due to very high risk of rejection, transmission of infection and toxicity of xenogenous tissue in human body. Allogenic precursor cells derived from bone marrow of healthy donors have been used in a randomized double-blind controlled trial [3]. This study met its primary objective – safety of allogeneic cells in the therapy of CLI and also showed a significant increase of ankle-brachial index (ABI) in treated group compared to placebo.