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Role of Cell Therapy for Patients with Chronic Critical Limb Ischemia to Prevent Amputation

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Editorial

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Editorial

Abbreviations: PAD: Peripheral Arterial Disease; ASO: Atherosclerotic Obliterans; CLI: Critical Limb Ischemia; BM-MNC: Bone Marrow Mononuclear Cells; IPS: Induced Pluripotent Stem; UCB: Umbilical Cord Blood; MSC: Mesenchymal Stem Cells; ABPI: Ankle-Brachial Pressure Index; ADRCs: Adipose-Derived Regenerative Cells

Peripheral arterial disease (PAD) is a condition where lumen of peripheral arteries are interrupted, narrowed or completely blocked. Reasons of PAD are Buerger's disease (Thromboangitis Obliterans, TAO), Atherosclerotic Obliterans (ASO) and connective tissue diseases. Additionally, ASO could be due to hypertension, hyperlipidemia and/or diabetes mellitus. Interruption of blood supply of peripheral arteries is a reason of ischemia. Severe rest pain and/or ulcerations of ischemic limbs are defined as the state of chronic critical limb ischemia (CLI). In patients with PAD with chronic CLI, surgical bypass and percutaneous trans-luminal angioplasty and combination with pharmacological therapy are options for revascularization and improvement in limb ischemic symptoms. Patients with no other conventional treatment option must undergo amputation. Of note, PAD with chronic CLI is the leading cause of amputation among the patients age over 50 years, and accounts for 90% of amputation worldwide.

Our study and study done by others shows that cell therapy involving implantation of bone-marrow or peripheral mononuclear cells is effective in patients with CLI with limited treatment options. Further analyses reveals that patients with Buerger's disease receiving bone marrow mononuclear cells (BM-MNC) implantation (n=26) had 95% major amputation free survival (MAFS) after 4 years, while it was only 6% in control (n=16) Buerger's patients (P<0.0001) [1-4]. Among the atherosclerotic PAD patients with BM-MNC implantation (n=25), MAFS after 4 years were 48% whereas no control (n=30) patients (0%) with atherosclerotic PAD could have 4 year MAFS (P<0.0001).[1]In TACT(Therapeutic Angiogenesis by Cell Transplantation) trial, patients with chronic limb ischemia (Fontaine stage III and IV, PAD due to ASO, n = 74 and Buerger's n = 41), three-year amputation-free rate was 60% in ASO and 91% in patients with Buerger's. Our study and study done by others reveal that autologous BM-MNC implantation improves endothelial function in patients with chronic CLI patients along with improvement of limb ischemic symptoms and findings of angiography [2,3]. BM-MNC implantation increases collateral vessel formation and improves ischemic symptoms in patients with CLI. Paracrine effect of bone marrow cells and/ or role of endothelial progenitor cells contained in bone marrow cells are considered the reason of healing.

It is evident that patients with Buerger's disease have superior outcome compared to the patients with ASO. Our study demonstrates that patients with Buerger's have better endothelial progenitor cell functionality compared to that of ASO [1]. Among patients with ASO, those having severe ASO and/or several comorbidities like end stage renal failure and diabetes mellitus have poorer outcome. In Japan, BM-MNC implantation is now carried out under advanced insurance program. However, not all the

patients with ASO can get benefit from the usage of BM-MNC implantation. Still a significant proportion of patients with chronic CLI need to undergo major amputation. And patients with ischaemic limb ulcers reaching until bone need at least minor amputation. These scenarios necessitate the development of further strategies for those patients.

One of the solutions could be usage of cells with higher regenerative potential. Although embryonic stem (ES) cells have pluripotent characteristics and can differentiate to various tissue types, ethical issues could be a hurdle to clinical use and inherent allogenicity of these cells will require administering long-term immune suppression in clinical subjects. There is also the risk of teratoma formation. Generation of patient-specific induced pluripotent stem (iPS) cells to overcome allogenicity is time-consuming, expensive and might be meaningless for urgent usage [5-6]. Umbilical Cord blood (UCB) cells also have some degree of pluripotentiality and can differentiate into various tissue types like the ES cells. Both in vitro and in vivo experiments proved that cord blood stem cells have the capacity to produce neural, epithelial, endothelial and hematopoietic tissues. It has been used for around 25 years to treat hematological disorders but no malignant transformation has been seen, except for instances where an abnormal gene is already present at the time of cord blood collection. Therefore, the pluripotency, ethical clarity and proven safety of UCB cells raised some optimism that it could be useful in critical limb ischaemia [6]. A phase 1 study done by Yang SS et.al, demonstrates that intramuscular human UCB driven mesenchymal stem cells (MSC) injection is a safe and well tolerated treatment for patients with chronic CLI due to ASO and Buerger's [7].

Exploration of Bone marrow derived mesenchymal stem cells (BM-MSC) might be another alternative for BM-MNC in chronic CLI patients. A prospective, double blind randomized placebo controlled multi-center study done by Gupta, et al. finds that BM-MSCs are safe when injected intra-muscularly at a dose of 2 million cells/kg body weight. Study was conducted among patients with chronic CLI not suitable for or had failed revascularization treatment and having Rutherford classification in category II-4, III-5, or III-6 with infra-inguinal arterial occlusive disease. Twenty patients received allogeneic BM-MSCs (n=10) or placebo (Plasma Lyte A, n=10) at the gastrocnemius muscle of the ischemic limb. Patients receiving BM-MSC showed significantly increased ankle – brachial pressure index (ABPI) and ankle pressure at 24 weeks [8].

Adipose-derived regenerative cells (ADRCs) are an encouraging alternative source of autologous somatic stem cells for regeneration of damaged tissue. Study done by Kondo K, et al. shows promising outcome and no major safety issues after usage of ADRCs for CLI patients although number of cases were six only [9].

In conclusion, autologous BM-MNC is one of the safe options to treat patients with chronic CLI. Usages of BM-MSC, UCB cells or ADRCs need ex-vivo manipulation. Therefore, safety concerns are needed to be addressed properly and further studies with large numbers of patients are needed to confirm initial outcome.

References

1. Idei N, Soga J, Hata T, Fujii Y, Chowdhury M, et al. (2011) Autologous Bone-Marrow Mononuclear Cell Implantation reduces Long-Term Major Amputation Risk in Patients with Critical Limb Ischemia: A Comparison of Atherosclerotic Peripheral Arterial Disease and Buërger's Disease. Circ Cardiovasc Interv 4(1): 15-25.

2. Higashi Y, Kimura M, Hara K, Noma K, Jitsuiki D, et al. (2004) Autologous bone-marrow mononuclear cell implantation improves endothelium-dependent vasodilation in patients with limb ischemia. Circulation 109(10): 1215-1218.

3. Yuyama TE, Matsubara H, Murohara T, Ikeda U, Shintani S, et al. (2002) Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. Lancet 360(9331): 427-435.

4. Pignon B, Sevestre MA, Kanagaratnam L, Pernod G, Stephan D, et al. (2017) Autologous Bone Marrow Mononuclear Cell Implantation and Its Impact on the Outcome of Patients With Critical Limb Ischemia - Results of a Randomized, Double-Blind, Placebo-Controlled Trial. Circ J 81(11): 1713-1720.

5. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, et al. (2009) Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 6(2): e1000029.

6. Chowdhury M, Hoque ME, Rajamanickam B, Hwang WYK (2013) Umbilical cord blood stem cells as a source of non-hematopoietic cells: role in

regenerative medicine. Regenerative Research 2(2): 1-7

7. Yang SS, Kim NR, Park KB, Do YS, Roh K, et al. (2013) A phase I study of human cord blood-derived mesenchymal stem cell therapy in patients with peripheral arterial occlusive disease. Int J Stem Cells 6(1): 37-44.

8. Gupta PK, Chullikana A, Parakh R, Desai S, Das A, et al. (2013) A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cell in critical limb ischemia. J Transl Med 11: 143.

9. Kondo K, Hayashida R, Shibata R, Murohara T (2016) Therapeutic Angiogenesis for Critical Limb Ischemia by Implantation of Autologous Adipose-Derived Regenerative Cells: A Clinical Pilot Study. Circulation 134: A18595.