

DRUG INFORMATION CENTER

PHARMA INFO-LINE

**STEM CELLS & THERAPEUTIC NEOVASCULARIZATION;
NEW HOPE IN PERIPHERAL ARTERY DISEASE**

In the last issue we made an introduction for the potential therapeutic applications of the stem cells. (read Drug Infoline, September 2007 issue 9).

In this issue we continue with one of these applications, which is the potential of stem cells for angiogenesis, that is formation of new blood vessels in patients with peripheral arterial disease.

Peripheral arterial diseases PAD

There are too many etiological causes for PAD the most prevalent of which is atherosclerosis (number one cause), and the two principal symptoms of which are;

⌘ Intermittent claudication, which is described as discomfort, pain, fatigue, or heaviness that is felt in the affected extremity during walking that resolves within a few minutes of resting.

⌘ Rest pain, which occurs when the blood supply does not adequately meet the basic nutritional requirements of the tissues of the affected extremity and pain typically, occurs in the toes or foot.

Furthermore persistent severe ischemia causes skin breakdown and leads to ulceration, necrosis, and gangrene with consequent need for amputation. Even minor trauma to an ischemic foot may produce a skin lesion that fails to heal[1].

Risk factors for PAD include; cigarette smoking, old age, elevated fibrinogen level, low HDL cholesterol, elevated systolic blood pressure and at last but not the least ;diabetes mellitus, which has crude incidence of PAD in 3.7 per 100 patient-year[2, 3].

The physiological basis for the use of the stem cells in the management of PAD;

in normal conditions when an organ is injured or become ischemic, in order to restore its function, the body will start to revascularize and regenerate the organ by the so-called angiogenic switch which involves recruitment of endothelial cells to form neo-vessels which consequently will form collateral pathway that compensate the original ischemic vessel [4].

However tissue injury in advanced age, diabetes and hypercholesterolemia is usually associated with disruption of a permissive microenvironment necessary for recruiting pre-existing endothelial cells, which leads to endothelial dysfunction; therefore the effort is now directed toward the introduction of exogenous vascular progenitor cells, and in order to prevent antigenicity; autologous cells (from the same person) are used, that can be obtained from bone marrow which is a rich reservoir of tissue – specific stem cells and progenitor cells.

The first preclinical (animal) study in this field was conducted by **Kalka et al**, (2000) in which they had transplanted human endothelial progenitor cells (hEPCs) to athymic nude mice (immunocompromized to prevent rejection) with hindlimb ischemia. hematopoietic stem cells (HSCs) were obtained from circulating blood and were used as an alternative to endothelial progenitor cells (EPCs) that is usually obtained from bone marrow. They described

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recovery in blood flow, they also reported that the capillary density in the ischemic hindlimb was markedly improved, and the rate of limb loss was significantly reduced. Therefore they concluded that Ex vivo expanded hEPCs may have utility as a "supply-side" strategy for therapeutic neovascularization[5].

Based on the previous findings in animal study, the first human randomized controlled trial was conducted by **Eriko Tateishi-Yuyama et al** (2002), in order to investigate efficacy and safety of autologous implantation of bone marrow-mononuclear cells in patients with ischaemic limbs that were caused by peripheral arterial disease. They also compared the angiogenic effect of bone marrow mononuclear cells versus that of peripheral blood mononuclear cells. The study which included 47 patients; was conducted in two steps, firstly; they did a pilot study, in which 25 patients (group A) with unilateral ischaemia of the leg were injected with bone marrow-mononuclear cells into the gastrocnemius of the ischaemic limb and with saline into the less ischaemic limb. Then they recruited 22 patients (group B) with bilateral leg ischaemia, who were randomly injected with bone marrow mononuclear cells in one leg and peripheral blood-mononuclear cells in the other as a control. The primary outcomes were safety and feasibility of treatment, based on ankle-brachial index (ABI) and rest pain. The authors found that at 4 weeks in (group B) patients, the ankle brachial index ABI was significantly improved in legs injected with bone marrow mononuclear cells compared with those injected with peripheral blood-mononuclear cells. Similar improvements were seen for all parameters to be monitored that prove efficacy of treatment such as; the transcutaneous oxygen pressure, rest pain and pain-free walking time. These improvements were sustained at 24 weeks. The author had also found similar improvements in (group A) patients. They interpreted these findings as follows; Autologous implantation of bone marrow mononuclear cells could be safe and more effective for achievement of therapeutic angiogenesis than peripheral -blood mononuclear cells, because of the natural ability of marrow cells to supply endothelial progenitor cells and to secrete various angiogenic factors or cytokines[6].

In response to these findings **Shoichi Inaba et al**(2002) ,reported their attempt for treating patients with atherosclerotic occlusion however using autologous peripheral blood

mononuclear cells. The study included seven patients, the mean age was 65.3 years and the mean bodyweight 58.6 kg. They were given granulocyte colony-stimulating factor (G-CSF) for 4 days subcutaneously in order to mobilize CD34 cells (endothelial progenitor cells) from the bone marrow, which are involved in angiogenesis. These cells were collected by apheresis and purified for only five out of seven patients in whom the CD34 ratio had increased to more than 0.1% of peripheral white cells. These CD34-enriched cells were injected at 50 points of limb muscle, with the patient under spinal anaesthesia, within a week of harvest.

The authors reported that all five patients recovered and parameters such as pain relief, and lengthening of maximum walking distance became apparent within a week of injection. These improvements continued more than a year later. However, objective tests of improvement, such as ankle-brachial pressure index and blood vessel change by angiography, were inconclusive, except for the disappearance of a heel ulcer in one patient. The authors concluded that their study indicated that autologous CD34 cells were effective as angiogenesis therapy[7].

In agreement with the use of peripheral blood mononuclear cells as alternative mean for bone marrow mononuclear cells, **Tohru Minamino et al**[(2002), have reported the result of their study in which they have done autologous implantation of peripheral-blood mononuclear cells in ischaemic limbs of three patients who progressively developed non-healing ulcers or gangrene with severe rest pain despite having undergone intensive treatments. 4 weeks after implantation, they noticed a significant increase in ankle-brachial pressure index (>0.1) in all patients. Rest pain in legs was greatly reduced in two of three patients, completely abolished in one patient. Additionally, they noticed a substantial improvement of ischaemic ulcers in two of three patients, suggesting that implantation of peripheral-blood mononuclear cells was similar to that of bone-marrow mononuclear cells. The advantages of the use of peripheral blood over bone marrow mononuclear cells as described by them are;

- Do not require general anaesthesia.
- Can be repeated easily[8].

Furthermore **Akio Ishida, et al** (2005) have studied the safety and feasibility of autologous peripheral blood mononuclear cells (PBMNCs) implantation after granulocyte-colony stimulating factor (G-CSF)-induced mobilization in patients

with severe peripheral arterial disease[9]. The study included six cases; 5 of thromboangitis obliterans and 1 of arteriosclerosis obliterans. The patients received G-CSF (10mg/kg/day), PBMNCs were harvested and injected intramuscularly for the patients with ischemia of the legs. The authors reported no serious adverse events related to G-CSF administration, while improvement in the ankle – brachial pressure index was seen in 4 patients at 4 weeks and ischemic ulcers improved in 3 of 3 patients. In addition the mean maximum walking distance significantly increased from 203 m to 559 m at 4 weeks and was sustained for 24 weeks. The authors concluded that implantation of PBMNCs collected after G-CSF administration could be an alternative therapeutic angioplasty in patients with severe PAD[9].

Conclusion:

Autologous bone marrow stem cells seems to be promising therapeutic option for the treatment of peripheral arterial diseases, which has initially shown efficacy in generation of new vessels in ischemic limb, improve quality of life and with good safety profile. In addition there are a growing number of case reports that supported the use of peripheral blood mononuclear cells as an alternative. Whereas, PBMNCs that contain CD34 have shown similar efficacy, however it needs prior G-CSF administration in order to mobilize the CD34 cells from the bone marrow to the blood, with consequent potential for adverse effects from this cytokine. Fortunately there were no serious adverse effects reported with this technique so far.

Furthermore, the use of PBMNCs that contains CD34 in therapeutic angiogenesis does not require general anesthesia, and can be repeated for the same patient, however we still need studies with large number of patients in order

to address the safety of the technique.

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DID YOU KNOW?

Formulary:

Originally referred to a book listing the ingredients and formula for making medicine. As the pharmaceutical companies took over the manufacturing task from the pharmacists, the term was used to refer to a list of those drugs that a hospital or other health care organization planned to carry in inventory. As drugs constitute a great part of the health care budget, institutions exert greater control over what did and what did not go into that list and became increasingly insistent that prescribers (clinicians) in these institutions pay attention to that list. The hospital pharmacy and therapeutic committees (PTC) that make inclusion decisions became an important part of its governance process. Now formularies are a normal adjunct to the managed care process. Hospitals have them, health plans have them and so do their pharmacy benefit managers (PBMs).

INFO-ALERTS DANGEROUS ABBREVIATIONS



Abbreviation	Intended meaning	Common Error
U	Units	Mistaken as a zero or a four (4) resulting in overdose. Also mistaken for "cc" (cubic centimeters) when poorly written.
µg	Micrograms	Mistaken for mg (milligrams) resulting in an overdose.
Q.D.	Latin abbreviation for every day	The full stop after the Q has sometimes been mistaken for an "I" and the drug has been given QID (four times a day) rather than once.
Q.O.D.	Latin abbreviation for every other day	Misinterpreted as "QD" daily or "QID" four times daily. If the "O" is poorly written, it looks like a full stop or "I".
SC or SQ	Subcutaneous injection	Mistaken as "SL" sublingual when poorly written.
TIW	Three times a week	Misinterpreted as three times a day or "twice a week)
D/C	Discharge; also discontinue	Patient's medications have been prematurely discontinued when D/C for discharge was interpreted discontinue as it is usually followed by medication names.
HS	Half strength	Misinterpreted as the latin abbreviation HS (hour of sleep)
Cc	Cubic centimeters	Mistaken as U (units when poorly written.
AU, AS, AD	Latin abbreviation for both ears; left ear; right ear	Misinterpreted as the latin abbreviation "OU" both eyes; OS "left eye"; OD (right eye)
IU	International unit	Mistaken as IV intravenous or as ten (10)
MS, MSO4, Mg SO4	Morphine sulfate or Magnesium sulfate	Confused for one another

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