Peripheral arterial disease is a common but under-recognized problem. As the disease progresses, the patient might suffer from rest pain and/or ischemic ulceration — critical limb ischemia (CLI). The primary goals for treating the limb symptoms of CLI are to improve functional capacity, exercise performance and qualify of life. Although numerous therapy options can be used for CLI, unfortunately, about 20-30% of patients with CLI cannot be treated successfully and the only option for them is often amputation. For this group of patients, there is a great need for alternative treatment strategies, and several strategies to stimulate new vessel formation are currently being tested. These include gene therapy, angiogenic cytokine therapy, and cell therapy (such as with bone marrow-derived mononuclear cells and endothelial progenitor cells). In preclinical studies, most of these therapies have promoted the development of collateral arteries and demonstrated beneficial effects in patients with CLI. However, a great deal of more clinical experience is needed to resolve safety concerns such as potentiation of pathological angiogenesis (e.g., malignancy) and so-called bystander effects of delivered factors (e.g., effects on kidney or atheroma). These concerns limit their clinical applications at the present time. Currently, extensive clinical trials on angiogenesis are underway in Japan and worldwide. However, most of the studies are neither placebo-controlled nor randomized. The focus of future research on collateral artery growth should shift back from exaggerated enthusiasm to clear, hypothesis-driven studies, hopefully providing better insights into the exact molecular mechanisms of postnatal vessel growth. Despite these hurdles on the way to clinical application, the stimulation of collateral artery growth undoubtedly remains one of the most exciting challenges facing the medical scientific community. Given the large number of patients that will benefit from such therapy, accomplishing this task would be a revolutionary step in cardiovascular medicine.

**Key Words:** Critical limb ischemia • Gene therapy • Growth factor therapy • Cell therapy • Stem cell therapy

**CLINICAL PROBLEMS AND AVAILABLE TREATMENT**

Peripheral arterial disease (PAD) is a common but
clude a variety of medical or surgical modalities as follows. Exercise training in a formal setting, revascularization with angioplasty and cilostazol all have proven efficacy. Prostaglandins do not have a documented role in treating claudication. Carnitine and its derivatives (propionyl-L-carnitine) have been shown to improve treadmill exercise performance and quality of life. These drugs also have an excellent safety profile. Statins have been demonstrated to not only reduce the increased risk of ischemic events but also appear to improve claudication symptoms. On the other hand, all patients with PAD should receive antiplatelet therapy to prevent ischemic events and angiotensin-converting enzyme inhibitors if appropriate. It is also recognized that selected patients with claudication symptoms may benefit from catheter-based interventions, and most PAD patients with critical leg ischemia require revascularization procedures. Although many therapies for claudication have been thoroughly investigated, unfortunately, about 20-30% of patients with CLI, such as those with no graftable distal vessels present, or neurologically impaired or hopelessly nonambulatory patients, cannot be treated by any of the methods as mentioned above and the only option for them is often amputation. For this group of patients, there is a great need for alternative treatment strategies. Several strategies to stimulate new vessel formation (i.e. arteriogenesis) are currently being tested.

EXPERIMENTAL AND ANIMAL STUDIES OF THERAPEUTIC ANGIOGENESIS

Three distinct mechanisms of new vessel formation have been identified: vasculogenesis, angiogenesis, and arteriogenesis. Numerous animal studies demonstrated the potential of a variety of experimental therapies in angiogenesis and vasculogenesis for ischemic diseases. These include gene therapy, angiogenic cytokine therapy, and cell therapy.

Growth factors and gene therapy: experimental evidence

A variety of genes and growth factors stimulate vascular cell proliferation and maturation with following angiogenesis. Some of them may enhance tissue regeneration not solely via the proangiogenic activity but also via promotion of stem/progenitor cell mobilization. Potential therapeutic genes or growth factors for improvement of angiogenesis or arteriogenesis include the target on vascular endothelial growth factor (VEGF, mobilization and differentiation of EPCs, and stimulation of endothelial cell proliferation), placenta-derived growth factor (PIGF, stimulation of ischemic tissue revascularization), fibroblast growth factor (FGF-stimulating growth of EPCs and smooth muscle cells), angiopoietin-1 (mobilization of EPCs and other progenitor cells), hepatocyte growth factor (HGF, stimulation of endothelial cells and attraction of tissue-resident cardiac stem cells), insulin-like growth factor (IGF-stimulating the growth of endothelial and smooth muscle cells, and progenitor cells), erythropoietin (mobilization of EPCs), and granulocyte monocyte-colony stimulating factor (GM-CSF, mobilization of stem cells and EPCs).

Results of preclinical studies have shown that angiogenic growth factors or genes encoding these proteins promote the development of collateral arteries, which is called therapeutic angiogenesis. Limited clinical data from protein-delivery and gene-delivery trials suggest that both approaches are safe. In view of the enclosure of formed mature vessels with periendothelial matrix and pericytes, smooth-muscle cells, or both, treatment with various angiogenic growth factors might be preferable in future treatments. However, a great deal more clinical experience is needed to resolve safety concerns such as potentiation of pathological angiogenesis (e.g., malignancy) and so-called bystander effects of delivered factors (e.g., effects on kidney or atheroma). Cell therapy for therapeutic vascularization

Bone marrow-derived mononuclear cells

Previous reports noted that bone marrow-derived mononuclear cells from adult humans improved capillary density in hindlimb ischemia. Bone marrow-derived mononuclear cell implantation into ischemic limbs promotes collateral vessel formation, with incorporation of endothelial progenitor cells into new capillaries. Matsubara and colleagues reported that a significant portion of the bone marrow-derived mononuclear cells synthesized not only angiogenic growth factors (VEGF and basic FGF) but also angiopoietin-1, interleukin 1β and tumour necrosis factor α, which are known to have important functions in maturation and maintenance of
the vascular system. Takakura and colleagues also reported that marrow hematopoietic cells release angiopoietin-1 to induce the maturation of endothelial progenitor cells. The multiple cytokines released by these bone marrow-derived mononuclear cells may also stimulate adequate enclosure of vessels by periendothelial matrix and pericytes, and smooth-muscle cells. These phenomena significantly improve the formation of stable capillary vessels.

Before extensively applying this therapeutic modality to human trials, one concern is that marrow cells could differentiate into various mesenchymal cells, since marrow cells include cells of various lineages, such as fibroblasts, osteoblasts, myogenic cells, and endothelial cells. However, animal studies showed that injected bone-marrow mononuclear cells are unlikely to have the ability to differentiate into fibroblasts, osteoblasts, and myogenic cells in ischemic tissues.

**Endothelial progenitor cells and postnatal vasculogenesis: experimental evidence**

Endothelial progenitor cells (EPCs) have recently been identified from adult species and shown to possess therapeutic potential in a variety of diseases caused by atherosclerosis. EPCs are mobilized from the bone marrow into the circulation, home to the site of vessel injury in response to physiological and pathological stimuli, and then differentiate into endothelial lineage cells, thus contributing to postnatal neovascularization. To date, EPCs have been applied in tissue engineering for improving the biocompatibility of vascular grafts, and have been demonstrated to preserve left ventricular function following myocardial ischemic injury.

The marker of angioblasts and hematopoietic stem cells, CD34, is used to isolate putative angioblasts from the leukocyte fraction of peripheral blood. Endothelial progenitor cells can also be isolated from human umbilical cord blood, bone marrow–derived mononuclear cells, and CD34+ or CD133+ hematopoietic stem cells. Importantly, EPCs can be successfully ex vivo expanded with the use of human peripheral blood mononuclear cells. Some of the EPCs were found to be able to differentiate into so-called late-outgrowth endothelial cells with expression of a panel of endothelial cell markers and uptake of Dil-acetylated LDL and binding of lectin. In animal models of ischemia, endothelial progenitor cells have been shown to incorporate into the formation of neovascularization in ischemic tissue with markedly improved blood flow recovery and capillary density and a reduced rate of limb loss.

**HUMAN CLINICAL TRIALS**

**Therapeutic vessel growth for critical ischemia: evidence from human trials**

**Growth factors and gene therapy**

In “no-option” patients with disabling ischemia despite all possibilities for medical or surgical revascularization therapies, the development of biological revascularization has been intentionally attempted with the use of recombinant growth factor proteins or gene therapy. The goal of therapeutic angiogenesis is to stimulate new blood vessel growth. Although there have not been many studies in peripheral artery disease, a few large randomized placebo-controlled trials have been performed in the adult heart to improve myocardial perfusion and function. The results of these trials can probably be applied to the therapy in patients with peripheral artery occlusion disease.

The FIRST study (FGF-2 Initiating Revascularization Support Trial) used basic FGF protein versus placebo. In the FIRST trial, 337 patients were randomized to a single intracoronary infusion of rFGF-2 at 0.3, 3, or 30 ug/kg or placebo. This study failed to demonstrate significant improvement at the end-points. Post hoc analysis suggested a significant improvement in exercise time only in patients over 65 years of age with severe ischemia symptoms. The VIVA trial (VEGF in Ischemia for Vascular Angiogenesis) used VEGF-1 protein. In the VIVA trial, 337 patients were randomized to a single intracoronary infusion of rhVEGF165 delivered via intracoronary infusion on day 0, followed by intravenous infusion on days 3, 6, and 9. At day 120, there was a significant improvement in an-
gina class. However, all other day 120 endpoints were not statistically different. The AGENT (Angiogenic GENe Therapy) trials tried replication-defective adenovirus containing the FGF4 gene (Ad5-FGF4). AGENT I and II showed that in the subset of patients with severe (class III or IV) angina, there were trends toward improvement. The trials reported that the Ad5FGF-4 treatment was well tolerated and did not result in any permanent adverse sequelae; however, primary end-points of efficiency were not reached. The REVASC study (Randomized Evaluation of VEGF for Angiogenesis in Severe Coronary disease), a phase II trial, is the first large randomized gene therapy trial, using replication-defective adenovirus containing the VEGF121 gene (AdVEGF121). The adenoviral-based vector was injected intramyocardially during surgery to 32 nooption patients. At 6-week follow-up, angina class dropped significantly in the treated group. However, 2 patients died due to postoperative complications in the treatment group.

In summary, these results suggest that a "single-shot" design with protein is not sufficient for therapeutic angiogenesis, since the half-life of protein is too short. On the other hand, most of the reports also suggested that single gene transfer for the majority of patients was ineffective.

Although current efforts are focused on targeting angiogenesis to ischemic tissues, there exists the theoretical risk of unwanted blood vessel growth in adjacent or distant tissue sites. VEGF is known to increase vascular permeability and tissue edema and to cause hypotension, while FGF therapy is associated with proteinuria. Broader safety concerns include the possibility of accelerating occult tumor growth, diabetic retinopathy, or atherosclerosis. These concerns limit their clinical applications at present.

### Table 1. Phase II clinical protein and gene therapy trials in patients with ischemic heart disease

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Protein or Vector</th>
<th>Route of Administration</th>
<th>No. of patients</th>
<th>Follow-up</th>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIRST</td>
<td>FGF-2</td>
<td>Intracoronary</td>
<td>337</td>
<td>90d to 6 mo</td>
<td>Negative (ET)</td>
<td>Negative (ETT)</td>
<td>44</td>
</tr>
<tr>
<td>VIVA</td>
<td>VEGF&lt;sub&gt;165&lt;/sub&gt;</td>
<td>Intracoronary</td>
<td>178</td>
<td>60, 120d, 1y</td>
<td>Negative (ET)</td>
<td>Negative (ETT)</td>
<td>45</td>
</tr>
<tr>
<td>Gene therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGENT II</td>
<td>FGF-4 (adenovirus)</td>
<td>Intracoronary</td>
<td>79</td>
<td>4 and 12 wk</td>
<td>Negative</td>
<td>Subgroup analysis positive (IDS, RPDS)</td>
<td>16</td>
</tr>
<tr>
<td>REVASC</td>
<td>VEGF&lt;sub&gt;121&lt;/sub&gt; (adenovirus)</td>
<td>Intramyocardial (surgery)</td>
<td>67</td>
<td>12, 26 weeks</td>
<td>Not defined</td>
<td>Positive (TET at 26 weeks)</td>
<td>46</td>
</tr>
</tbody>
</table>

AC, angina class; ABI, ankle-brachial index; ET, exercise tolerance; ETT, exercise treadmill test; FGF, fibroblast growth factor; MP, myocardial perfusion; IDS, ischemic defect size; RPDS, reversible perfusion defect size; TET, time to ST depression on exercise tolerance; VEGF, vascular endothelial growth factor.
The intriguing results from experimental studies of gene and protein therapy as mentioned above promoted the initiation of clinical cell therapy pilot trials. In 2002, Tateishi-Yuyama et al. and the Therapeutic Angiogenesis by Cell Transplantation (TACT) study investigators performed a randomized controlled trial in patients with PAD. These investigators found that, after intramuscular injection of bone marrow-derived mononuclear cells, a significant increase in transcutaneous oxygen pressure, rest pain, and pain-free walking time was noted in most of the patients with leg ischemia.

The success of bone marrow-derived mononuclear cells in the treatment of critical limb ischemia is well explained as follows. Bone marrow-derived mononuclear cells contain both CD34+ and CD34− fractions. Endothelial progenitor cells in the CD34+ stem-cell fraction take part in postnatal neovascularisation.55,56 Infusion of endothelial progenitor cells has been shown to induce angiogenesis in ischemic limbs.57,58 This line of evidence can be supported by the findings that peripheral blood-derived mononuclear cells devoid of endothelial progenitor cells had weaker angiogenic activity. Knowledge gained from studies in the past few years suggests that efficacy of implantation of bone marrow-derived mononuclear cells is due to supply of endothelial progenitor cells (included in CD34+ fraction) and multiple angiogenic factors (released from CD34− fraction). The CD34− fraction in bone marrow-derived mononuclear cells synthesized not only angiogenic growth factors (VEGF and basic FGF) but also angiopoietin-1, which is known to have important functions in maturation and maintenance of the vascular system.33,59 When considering clinical potential of therapeutic angiogenesis, for newly formed vessels to survive, they must be remodelled and acquire a smooth-muscle coat with adequate enclosure of vessels by periendothelial matrix and pericytes, and smooth-muscle cells.60 These combined effects derived from bone marrow-mononuclear cells, mixing CD34+ and CD34−, could lead to the formation of stable capillary vessels.

As mentioned regarding the animal studies, marrow cells include cells of various lineages. Such mixed popu-

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Protein or Vector</th>
<th>Delivery method</th>
<th>No. of patients (disease)</th>
<th>Follow-up</th>
<th>Results</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Protein therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAFFIC</td>
<td>rFGF-2</td>
<td>Intra-arterial</td>
<td>174</td>
<td>3 months</td>
<td>Negative*</td>
<td>47</td>
</tr>
<tr>
<td>Hisayoshi et al.</td>
<td>G-CSF</td>
<td>Intra-venous</td>
<td>N.A.</td>
<td>Ongoing</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Masazumi et al.</td>
<td>G-CSF</td>
<td>Intra-venous</td>
<td>N.A.</td>
<td>Ongoing</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Yoshikazu et al.</td>
<td>bFGF/FGF-2</td>
<td>Intra-muscular</td>
<td>N.A.</td>
<td>Ongoing</td>
<td>Negative*</td>
<td></td>
</tr>
<tr>
<td>Gene therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVE</td>
<td>VEGF</td>
<td>Intra-muscular</td>
<td>105</td>
<td>12, 26 months</td>
<td>Negative (ET, QOL)</td>
<td>15</td>
</tr>
<tr>
<td>TREAT-HGF</td>
<td>HGF</td>
<td>Intra-muscular</td>
<td>N.A.</td>
<td>Ongoing</td>
<td>Negative (ET, QOL)</td>
<td></td>
</tr>
<tr>
<td>Cell therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACT</td>
<td>BMC</td>
<td>Intra-muscular</td>
<td>45</td>
<td>3 months</td>
<td>Positive (ET, QOL)</td>
<td>22</td>
</tr>
<tr>
<td>Kudo</td>
<td>EPC</td>
<td>Intra-muscular</td>
<td>2</td>
<td>2 weeks</td>
<td>Positive (TcPO2)</td>
<td>51</td>
</tr>
<tr>
<td>Atsuiko et al.</td>
<td>EPC</td>
<td>Intra-muscular</td>
<td>N.A.</td>
<td>Ongoing</td>
<td>N.A.</td>
<td></td>
</tr>
</tbody>
</table>

BMC, bone marrow cell; bFGF, basic fibroblast growth factor; ET, exercise tolerance; G-CSF, granulocyte-colony stimulating factor; HGF, hepatic growth factor; TcPO₂, transcutaneous oxygen pressure; VEGF, vascular endothelial growth factor; QOL, quality of life. *, positive after evaluating 190 patients.
lations could differentiate into various mesenchymal
cells.\textsuperscript{24} In the TACT study, investigators immunohisto-
chemically investigated marrow-implanted limbs. Appar-
etent increases in capillary numbers were noted, whereas
neither bone formation nor increased interstitial fibrosis
was detected. Thus, in ischemic limbs, endothelial-line-
age cells could effectively differentiate into mature cells,
whereas some survival factors to stabilise other mar-
row-derived lineage cells could be lacking in ischemic
conditions. On the other hand, the TACT study demon-
strated that marrow implantation did not affect circulating
concentrations of angiogenic growth factors. Combin-
atetions of these growth factors locally secreted from the
marrow cells might be useful in further treatments di-
rected toward neovascularisation of tissues without ad-
verse effect on retinopathy or the concerns on tumor
growth.

Regarding use of the circulating endothelial progeni-
tor cells from peripheral blood as a more convenient
source, Kudo and colleagues have been investigating the
use of autologous transplantation of peripheral blood en-
dothelial progenitor cells for therapeutic angiogenesis in
patients with critical limb ischemia.\textsuperscript{53} However, to ac-
chieve a functional improvement, endothelial progenitor
cells needed to be ex vivo cultured to enrich an active
subpopulation (which is maximally approximately 0.5%
of the total mononuclear cells) out of the peripheral blo-
d mononuclear cells. Otherwise, freshly isolated EPC-
containing peripheral blood monocytes did not exert any
effect. This process raises the safety concern over the
implantation of ex vivo cultured cells back to ischemic
tissues and hampers its clinical applications at the cur-
rent stage.

Some investigators have been trying to increase the
mobilization of endothelial progenitor cells to circulation
before harvesting from peripheral blood. Pretreatment
with G-CSF can increase endothelial progenitor cells in
bone marrow or peripheral blood, which could reduce
the aspiration volume of marrow cells required or en-
\hance efficacy of collateral vessel formation after im-
plantation of bone marrow-mononuclear cells. In two re-
ports, injection of GM-CSF was noted to mobilise endo-
thelial progenitor cells from bone marrow\textsuperscript{54} or promote
cardiac collateral growth in patients with coronary artery
disease.\textsuperscript{55} However, angina pectoris or acute\textsuperscript{56} arterial
thrombosis\textsuperscript{57} arise in patients receiving G-CSF (granu-
locyte-colony stimulating factor) because of leucocytosis
or hypercoagulability. Since most patients eligible for
cell therapy are predicted to have severe atherosclerotic
lesions in coronary or cerebral arteries, pretreatment
with G-CSF might cause deleterious vascular events be-
fore angiogenic cell therapy. On the basis of these find-
ings, clinical trial adopting pretreatment with these fac-
tors raises safety concerns.

Although increased perfusion was demonstrated in
most of the studies as described above, these studies at
present are limited by the small patient samples and by
the design of pilot safety and feasibility studies.\textsuperscript{58-61} The
TACT study\textsuperscript{25} is the first to show the efficacy and safety
of implantation of bone marrow-derived mononuclear
cells in 45 ischemic limbs. Legs that were injected with
peripheral blood-derived mononuclear cells showed much
smaller increases in collateral perfusion, suggesting in
favor of bone marrow-derived mononuclear cells as an
effective therapeutic strategy. Furthermore, autologous
implantation of bone marrow-mononuclear cells can also
constitute a safe strategy for achievement of therapeutic
angiogenesis without cell rejection.

\section*{CURRENT STATUS OF THERAPEUTIC
TRIALS IN A CLINICAL SETTING}

Currently, in addition to the bone marrow implan-
tation strategies mentioned above, extensive clinical trials
on angiogenesis are ongoing in Japan and worldwide
(Table 2). These clinical trials include: (1) Endothelial
progenitor cells in Angiogenesis: Dr. Kawamoto Atsuhiko
(Japan); Dr. Asahara (Japan); (2) Hepatocyte growth fac-
tor in angiogenesis — TREAT-HGF (Japan trial to Treat
Peripheral Arterial Disease by Therapeutic Angiogenesis
Using Hepatocyte Growth Factor Gene Transfer); (3)
G-CSF in Angiogenesis: Dr. Fujiwara Hisayoshi (Ja-
pan); Dr. Arai Masazumi (Japan); (4) bFGF/FGF-2 trials
in Angiogenesis: Dr. Yonemitsu Yoshikazu (Japan). How-
ever, all these studies are right in the middle of their
courses and not finished. Unpublished data has shown
promising effects based on these treatment modalities,
however, safety results have not been released yet (The
37\textsuperscript{th} Japan Atherosclerosis Society Annual Meeting.
WellVAS 2005;11).

The TACT study proved that autologous implantation

\textbf{Acta Cardiol Sin 2006;22:187–97}
of bone marrow-derived mononuclear cells could be safe and effective for achievement of therapeutic angiogenesis in patients with ischemic limbs because of PAD. After this report was published, Dr. Matsubara organized more than 20 medical centers in Japan to undertake an extensive clinical trial based on the same therapeutic strategy. Unpublished data showed that this strategy generally caused a 65% improve in ankle-brachial index, an 80% improve in rest pain, 3 minutes longer pain-free walking time, and, most importantly, a 75% decrease in amputation rate and a 60% improve in limb ulceration (The 37th Japan Atherosclerosis Society Annual Meeting. WellV AS 2005;11). Additionally, with regard to adverse effects associated with this intervention, no infection, inflammation or increases of any specific systemic cytokines have been noted or reported. The procedure of bone marrow aspiration is just a regular procedure for hematologists doing bone marrow transplantation and can be safely performed by experienced hands without safety issues. The only supportive treatment is for those patients with Hb < 10 gm/dl, who need blood transfusion after bone marrow aspiration. Basically, this therapeutic procedure is perfectly acceptable on safety grounds.

Given the findings that transplantation with whole bone marrow cells holds promise in the efficacy of cell therapy for critical limb ischemia, there may be a future attempt to mix a few different populations of potential cells for cell transplantation. Recently, Yoon et al. cultured different types of endothelial progenitor cells from peripheral mononuclear cells. These different populations produced beneficial profiles of cytokines and proteases with synergistic impacts on neovascularization. The transplantation of mixed types of cells resulted in synergistic augmentation of angiogenesis. Rafii and Lyden et al. also supported that such synergistic interactions may be present among a variety of stem or progenitor cells, possibly shedding light on a future direction of stem cell therapy.

However, as mentioned above, most of the early trials evaluating the stimulation of vascular growth were neither placebo-controlled nor randomized. The focus of future research on collateral artery growth should shift back from exaggerated enthusiasm to clear, hypothesis-driven studies, hopefully providing better insights into the exact molecular mechanisms of postnatal vessel growth. Actually, only class IIb indication is granted for angiogenic growth factor therapy for peripheral artery disease in the recent 2006 AHA guidelines. Despite these hurdles on the way to clinical application, the stimulation of collateral artery growth undoubtedly remains one of the most exciting challenges facing the medical scientific community. Given the large number of patients that will benefit from such therapy, accomplishing this task would be a revolutionary step in cardiovascular medicine.

QUALITY OF PRACTICE AND CONCERNS OF COST AND BENEFIT

More and more new strategies for the treatment of peripheral artery occlusive disease are being designed. Cell therapy holds great promise for improving peripheral ischemia in the future. However, when new cell therapies are being developed, it must be kept in mind that we have to perform all the possible treatments in line with the guidelines of good laboratory practice (GLP), good clinical practice (GCP), and good tissue preparation. GLP briefly contains two parts, namely, the hardware and the software. The hardware includes tissue or cell harvesting, isolation, preservation and delivery systems. The software means the responsibility to manage the research database, including projects, papers, awards and patents, under the guidelines of GCP at the same time.

The costs and benefits, and the advantages and disadvantages, of an alternative therapy should be considered when adopting a new treatment strategy for a patient. For example, the procedures of cell therapy with whole BMCs include BM aspiration, general anesthesia, cell separation and cell injection. Generally, it costs around NTS 22,000 per patient. The disadvantages are that the patient has to take the risk of general anesthesia and BM aspiration, and that the expenditure is higher than that for an angioplasty procedure (approximately NTS 10800-13000 per angioplasty). However, these new angiogenesis strategies, of course, have benefits in a “non-option” patient before a limb amputation is performed.

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3009-17.
週邊動脈血管疾病是一個常見但往往不容易被發現的問題，隨著疾病的進展，這些病人可能會有休息時疼痛或者是缺氧性潰瘍的發生，我們稱之為嚴重肢體缺氧。治療這種病人的基本目的就是要改善他們的功能狀態、運動能力以及生活品質。雖然目前對於這種嚴重肢端缺氧的病人有相當多的治療方法，但是不幸的仍有多數的病人治療無效而必須接受截肢手術。對於這一類的病人有極大的需要去發展新的治療方法來刺激新生血管的形成以改善缺氧情形。這些方法包括基因治療、成長素治療或是細胞治療，例如幹細胞治療。目前研究顯示大部分這些新的治療方法似乎都可改善缺氧狀態，但是隨著治療所帶來的一些副作用和一些意想不到的不良效果則是我們必須注意的安全考量，這些安全考量也大大的限制了新治療方法的臨床應用。目前全世界有大量的臨床試驗及研究在進行中，然而大部分這些臨床試驗及研究並未使用安慰劑控制型的或是隨機型的，將來的研究設計應該更為嚴謹以提供更正確的資訊。雖在應用到臨床治療方面的困難相當多，但是基於全世界有龐大數目的病人可能會受益於這些治療，若能夠克服這些困難將是在心臟血管醫療史上革命性的進展。

關鍵詞：嚴重肢體缺氧、基因治療、成長素治療、細胞治療、幹細胞治療。