The treatment of advanced chronic lower limb ischaemia with marrow stem cell autotransplantation

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Abstract

Introduction: Conventional methods of critical leg ischaemia treatment are of limited efficacy. Amputation, as an ultimate solution, is not so rare. The results of marrow stem cell therapy as a potential novel approach to peripheral artery disease management were presented in 2002 by Tateishi-Yuyamy.

Aim: To assess efficacy and safety of critical lower limb ischaemia treatment with marrow stem cell autotransplantation.

Methods: Ten patients suffering from chronic leg ischaemia in Fontaine IV stadium were involved in the study. They did not require emergency amputation and had previously been unsuccessfully treated with conventional therapy. Autologic marrow stem cells were condensated by a separator from bone marrow samples taken from the iliac crest. The cells were delivered intramuscularly by repeated injections into the pedal and tibial regions. The number of CD34 and AC133 positive mononuclear cells in each sample was evaluated by flow cytometry. After two weeks and one, two, three and twelve months the following parameters were measured: Laser Doppler Flux (LDF), percutaneous oxygen partial pressure, ankle-brachial index (ABI), visual analgesic scale (VAS), analgesic therapy requirement and ulceration area. Also, lower leg angiography and scintigraphy were performed.

Results: An improvement of the peripheral blood flow assessed by Laser Doppler Flux and percutaneous oxygen partial pressure was found. Pain severity decreased in the majority of patients. Amputation was required in three patients in whom the therapy failed. No side effects of the therapy were observed. The clinical effect of the treatment did not correlate with the amount of cells injected.

Conclusion: Marrow stem cell autotransplantation into the ischaemic lower limb seems to be a potentially effective method of peripheral perfusion enhancement. Further studies are needed to clarify the underlying mechanisms of such improvement.

Key words: angiogenesis, neovascularisation, critical leg ischaemia, atherosclerosis obliterans, marrow stem cells.

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Introduction

The differentiation process of marrow stem cells into vascular or muscular cells was a milestone discovery for angiogenesis research. Attempts were made to control the angiogenetic processes to treat ischaemia of different organs. Cells, being able to transform in extramedullar tissues, belong to mononuclears. These cells are characterised by molecules found on their surface, such as CD34 [1-3].

They are released from the marrow compartment into the peripheral blood [4, 5]. Their amount in healthy adults ranges from 5 to 40 cells per mm^3 of blood [4, 5]. A chronic inflammatory process leads to their nearly

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complete disappearance from the circulating blood. A marked increase of these cells is observed in acute tissue ischaemia or after the granulocyte colony stimulating factor (G-CSF) is given. Stem cells are found in most extramedullar organs, where they belong to the *reserve pool*. These cells may transform into functional ones, which replace the damaged units.

The chain of reactions that leads to neovascularisation remains unknown. The cells seem to play an important role in this process, though the role of cytokines and growth factors should also be emphasised. These molecules are released not only by cells of marrow origin, but also other cells [6-9].

Isolation of stem cells and their implantation has been successfully conducted in animal models of myocardial ischaemia. This method was shown to be effective in perfusion restoration and contractility preservation [10, 11]. Therapeutic considerations are inspiring clinical trials focusing on heart muscle perfusion and contractility improvement in cases of acute or chronic ischaemia [12, 13].

Professors T. Siminiak and M. Kurpisz, pioneers in this scientific field in Poland, launched studies investigating experimental treatments of ischaemic heart disease with myoblasts (obtained from the patient's femoral muscle). The results of the trials received international attention [14, 15].

Stem cells are also being tested in post-stroke brain injury and in experimental treatments of other organ dysfunctions [16].

In clinical trials stem cells are isolated using one of the following techniques:

1. direct marrow aspiration [17];
2. isolation from the peripheral blood after exogenous stimulation with G-CSF or GM-CSF [18].

The main disadvantage of the former method is that a large amount (a few hundred ml) of the bone marrow must be aspirated under general anaesthesia. In the alternative, the use of growth factors is controversial, as their safety has never been defined. Angina and arterial thrombosis after growth factor administration have been documented [19, 20] and proatherogenic and carcinogenic effects have been suggested. Thus, the aspiration method seems to be a safer alternative.

While there is a wide range of reports on severe ischaemic heart disease treatment with marrow stem cell administration, only a few focus on a similar approach to leg ischaemia management. The only report presenting the results of such treatment has been published by Tateishi-Yuyama et al. [17]. They reported complete resting pain relief in 22 cases and partial relief in 15, and the amelioration of ulcerations in 6 out of 10 patients after stem cell administration. Hallux amputation was avoided in 15 of 20 cases.

A correlation between the CD34 cell dose and in vivo angiogenesis effects was observed by Osamu Iber et al. [21]. Thus, there is a reasonable question whether regularly repeated doses may lead to better short- and long-lasting therapeutic effects.

The aim of this paper is to present preliminary data on safety and efficacy of peripheral ischaemia treatment with autologous marrow cell transplantation.

Methods

Patients

Ten patients were enrolled into the study (4 women and 6 men, mean age of 48.7 yrs., SD: 11.7). They suffered from critical leg ischaemia due to thrombotic obliterative vasculitis (7 cases) or arteriosclerosis obliterans (3 patients) of the lower extremities (Table I). All these patients were previously disqualified from either surgical revascularisation, endovascular intervention or sympatectomy and had no indications for emergency amputation. All the patients had critical leg ischaemia (CLI) symptoms lasting for at least eight weeks. Each of them presented with active ulceration or gangrene (Fontaine stadium IV). All had continuous or recurring rest pain and required analgesia.

All patients had to sign an informed consent form to participate in the study. The exclusion criteria were as follows: concomitant disease precluding bone marrow aspiration under general anaesthesia, life expectancy shorter than 12 months, diabetes mellitus, cancer, active autoimmune process or active vasculitis.

There were two patients who underwent unsuccessful surgical revascularisation in the preceding months and neither was treated by endovascular intervention. Arterial hypertension was diagnosed in three patients with arteriosclerosis obliterans and two patients suffered from ischaemic heart disease with stable angina of CCS class II.

The study was approved by the Bioethical Committee of Collegium Medicum, Jagiellonian University.

Marrow stem cell autotransplantation

About 500 ml of marrow aspirate was withdrawn from the iliac crest under general anaesthesia. From each aspirate after centrifugal sedimentation in a cellular separator (CS3000-Plus, Baxter, USA) 45 ml of the concentrate, rich in mononuclears, was obtained. Three to four hours after marrow aspiration, the concentrate was injected intramuscularly into the lower leg or foot (in one case into the hand and forearm). The volume of each injection was 0.5 ml (approximately 90 injections, of 1.5 cm depth). The injections were applied over the area in the nodes of a 3x3 cm grid.

Table I. Patient characteristics

	ID	Age	Gender	Cause	Localisation	Clinical presentation
1	AJ	46	F	Buerger	foot	ulceration
2	DB	43	F	Buerger	foot	ulceration
3	LB	37	F	Buerger	foot	ulceration
4	KB	58	M	PAOD	foot	gangrene
5	CJ	45	M	Buerger	hand	gangrene
6	SH	52	M	PAOD	foot	gangrene
7	SS	38	M	Buerger	foot	ulceration
8	BA	42	M	Buerger	foot	ulceration
9	NM	49	M	Buerger	foot	ulceration
10	ZM	77	F	PAOD	foot	gangrene

PAOD – arteriosclerosis obliterans; Buerger – thrombotic obliterative vasculitis

The average number of implanted mononuclears was $3.28x10^9$ (SD±$2.19x10^9$). The average number of the CD34 cells was $6.35x10^7$ (max. $8.1x10^7$, min. $0.4x10^7$). The CD34 cells usually accounted for 1.89% (SD±1.52) of leucocytes in every specimen.

Other treatment

The patients were managed according to the guidelines for the treatment of leg ischaemia caused by thrombotic occluding vasculitis or arteriosclerosis obliterans. Only drugs directly affecting the stem cell functions were excluded (ablative or stimulating, such as G-CSF or GM-CSF). Vasoactive agents (i.e. allprostil, prostacycline analogues) were not used; nor were surgical, endovascular or sympatectomy techniques applied. The gangrene or ulcerations were managed typically with local treatments. In cases of symptoms of local infection, systemic antimicrobial therapy was used. Baseline assessment of patients was performed two weeks before the intervention and after two and four weeks as well as 3, 6 and 12 months postoperatively.

Assessed parameters

The following parameters were measured at baseline and during the follow-up:

1. Ankle-brachial index (ABI). According to international standards an increase of at least 0.1 was recognized as a significant improvement and a value >0.9 was regarded as normal.
2. Cutaneous blood flow measured by laser Doppler flux (LDF) was defined as the sum of the measurements obtained from five different locations: dorsal side of the foot at the level of the head of the 1st and 5th metatarsal bones, at the level of the base of the 2nd metatarsal bone and 2 cm below the medial and lateral ankle. Every parameter was measured in similar conditions: ambient temperature of 20°C, seated patient, after 5 min. rest.
3. Percutaneus partial oxygen pressure ($tcp0_2$) was measured with the Oxymeter Novametrix (USA). The

Table II. Baseline assessment – target (intervention) *vs* contralateral (no intervention) limb

	intervention mean ±SD	no intervention mean ±SD	p
ABI	0.39 (0.28)	0.80 (0.13)	0.003
LDF [PU]	20.5 (8.3)	97.7 (29.2)	0.025
$TCPO_2$ [mmHg]	21.7 (17.3)	53 (10.4)	0.002

Abbreviations:
ABI – ankle-brachial index; LDF=Laser Doppler flux;
$TCPO_2$ – percutaneous partial oxygen pressure

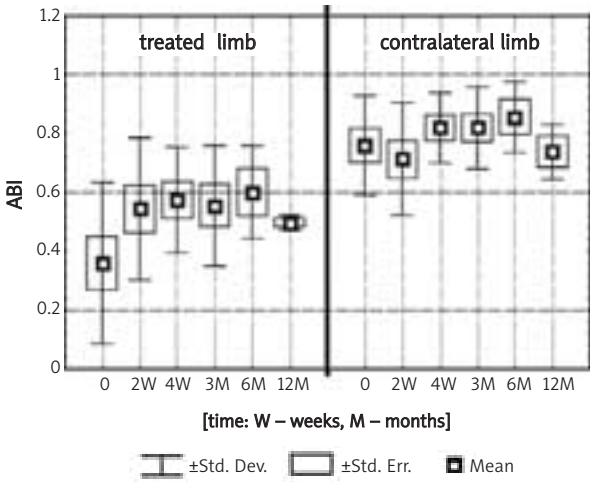

Figure 1. Ankle-brachial index (ABI) in treated and contralateral (untreated) limb

Table III. Baseline *vs* follow up at 3 months

	limb – intervention				limb – no intervention			
	baseline mean ±SD	+3M mean ±SD	change	p	baseline mean ±SD	+3M mean ±SD	change	p
ABI	0.39 (0.28)	0.55 (0.2)	+0.17	0.015	0.80 (0.13)	0.82 (0.14)	+0.02	0.31
LDF [PU]	20.5 (8.3)	87.7 (37)	+67.2	0.043	97.7 (29.2)	84.2 (39.1)	-13.5	0.5
$TCPO_2$ [mmHg]	21.7 (17.3)	36.5 (23.8)	+14.75	0.002	53 (10.4)	51(7.7)	-2.0	0.73
VAS	74.4 (14.1)	43.1 (29.1)	-31.2	0.008				

Abbreviations:
VAS – visual analogye scale; rest of abbreviations – as in Table II

measurements were taken half way between the hallux base and the lateral ankle. At the hand, the device was placed half way between the base of the 5th and 1st finger. The operational temperature of the probe was 44°C. Every parameter was measured in similar conditions: ambient temperature of 20°C, horizontal position, after 5 min. rest, patient breathing normal air. The mean value of 15 minutes' stable recording was used as a result for further analysis (normal value ≥60 mmHg).

4. The arterial angiography was performed twice (2 weeks before and 3 months after the procedure). Both examinations in each patient were carried out with identical settings (type, amount and mode of delivery of contrast agent, catheter position, lamp distance, angle and emission). The angiograms were evaluated by an experienced interventional angiologist, not involved directly in the programme.
5. Every patient underwent a radionuclide lower limb perfusion scan before and at three months after the procedure. During the phase of maximum hyperaemia an intravenous 370 MBq Tc^{99m} MIBI was injected. Whole body radiation was recorded by two-head camera Phillips Axis (*whole body acquisition mode*). After having calculated the amount of radiation from the target extremity, the tibial and foot muscle perfusion indices were derived by dividing the target area and whole body radioactivity (expressed as percentages).
6. If ulceration of the lower limb was present, its area was measured.
7. Severity of pain was self-assessed by patients using a visual analogue scale (VAS). No pain at all was rated 0, maximum pain 100.
8. Daily requirement for the analgesics was calculated as a mean from the last seven days prior to the assessment (mg/24 h).

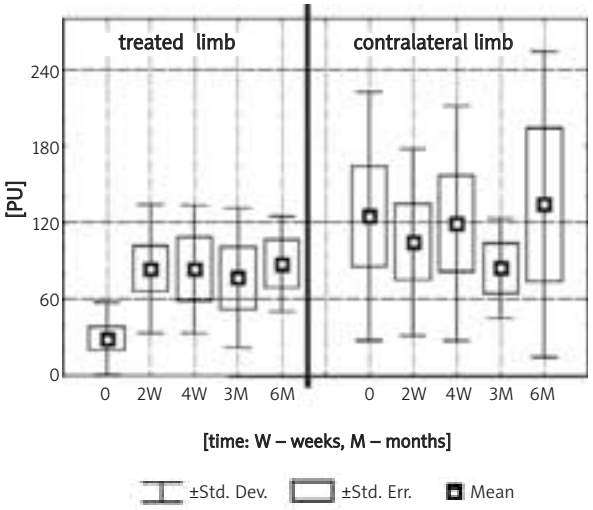

Figure 2. Laser Doppler flux values in treated and contralateral (untreated) limb

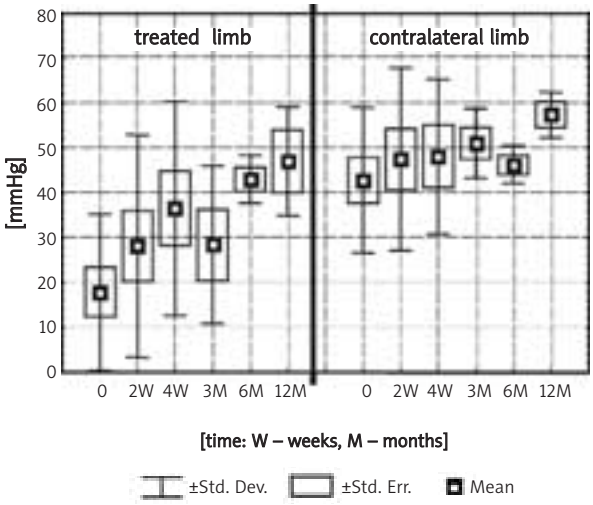

Figure 3. Oxygen partial pressure ($TCPO_2$) in treated and contralateral (untreated) limb

Statistical analysis

Paired t-test was used to evaluate the differences between the clusters of measurements taken at individual time points. A p value of less than 0.05 was considered significant.

Results

In January 2005 six patients completed the planned 12-month follow-up. One patient was followed for six months and another three patients for three months. The therapy failed in three patients in whom gangrene progression resulted in limb amputation, at 12 weeks in A.J., at 8 weeks in SH and 3 weeks in Z.M. In four of six patients, who reached 12-month follow-up, the limb was functioning well. At baseline there were significant differences of haemodynamic parameters of target and contralateral legs (Table II).

Rapid and significant reduction of pain severity was observed within days (with unchanged or reduced requirement for analgesics). Haemodynamic parameters also improved significantly within the first few weeks of follow-up. Changes of each parameter were most dynamic in the first month, then relatively small (Figures 1, 2, 3; Table III).

In the contralateral limbs no haemodynamic changes were detected (Figures 1, 2, 3; Table III).

In the majority of patients a decrease of pain severity was observed within the first few days after the procedure as evidenced by a reduced VAS score (Figure 4). Pain relief tended to be stable over 12-month follow-up (Figure 4). The patients who underwent leg amputation were excluded from the pain and analgesics use analysis at time points following the amputation. Pain severity reduction was accompanied by lower daily consumption of analgesics (Figure 5). In three subjects in whom therapy failed daily consumption was similar to baseline or even higher (Figure 6). Beneficial changes of objective parameters (BI, LDF, and tcpO2) corresponded with clinical improvement evidenced by a reduction in the ulceration area (Figure 7-12).

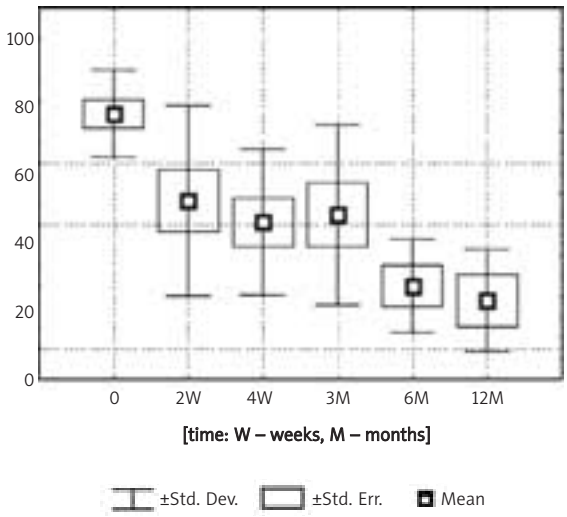

Figure 4. Pain perception scale values during follow-up

Angiographic results

At baseline, advanced atherosclerotic changes were detected in the vessels of the lower leg and foot (in one case of the forearm and hand). We faced methodological difficulties comparing pre- and post-procedural angiograms. No reliable, reproducible and objective method of comparative angiographic assessment of angiogenesis and vasculogenesis has been developed so far [17]. The angiographic images hardly ever provide a definite answer to the question of whether detectable neoangiogenesis is really present. Only in one case (KB patient) was the improvement in vascular net density in the third month angiogram evident. Diameters of vessels

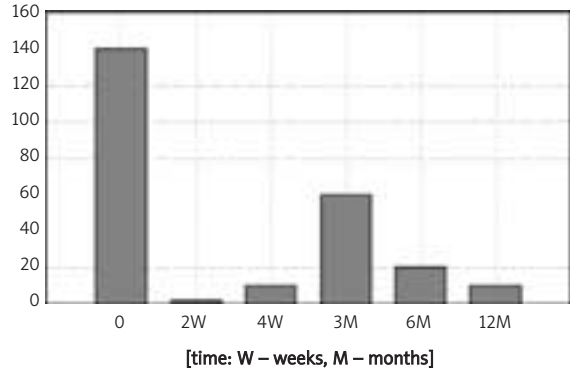

Figure 5. Daily analgesic consumption in patient LB

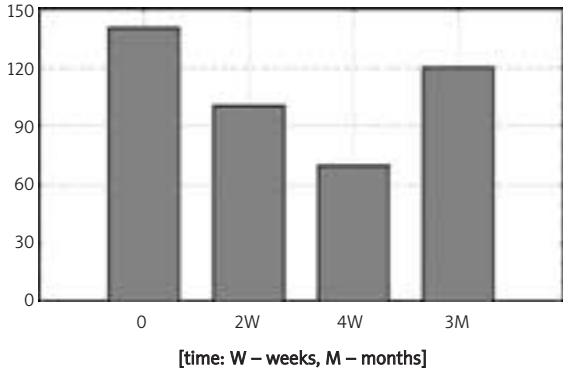

Figure 6. Daily analgesic consumption in patient AJ

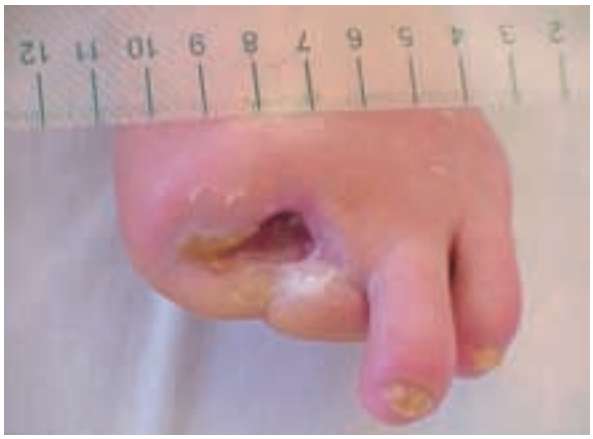

Figure 7. LB at baseline

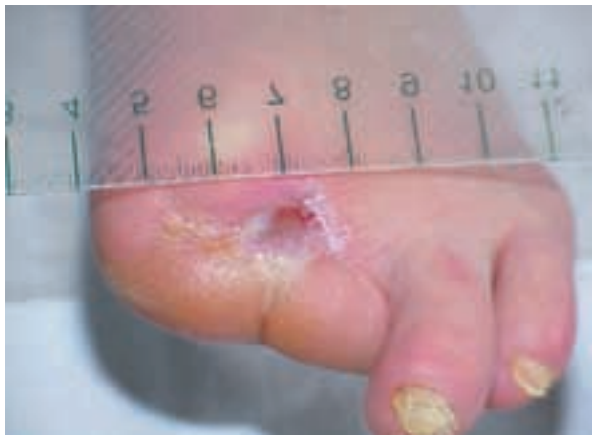

Figure 8. LB after 12 months

existing at baseline/existing vessels at baseline increased and new collaterals were seen on the angiogram (Figures 13, 14 – arrows).

The perfusion index of the target leg in LB, SS and KB patients increased significantly at three months by 14.9%, 4.53% and 16%, respectively (Figure 15). In the case of patient AJ, who required amputation in the 12th post-procedural week, the perfusion index decreased by 9.86% (Figure 16). In other cases, there were either no differences between examinations or legs were amputated before the third month of follow-up (SH, ZM).

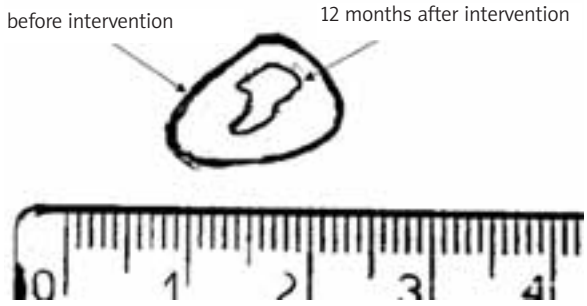

Figure 9. LB Ulceration area changes

Discussion

Before transplantation, the targeted limbs were definitively less perfused than contralateral ones. Presented data suggest a significant improvement in the peripheral circulation in the limbs subjected to the treatment as compared with unchanged perfusion of contralateral ones. The amelioration was detected not only by haemodynamic indices (ABI, tcpO2, LDF), but also by clinical status changes expressed as a decrease in pain severity and consumption of analgesics. These beneficial effects were stable during the whole 12 months of follow-up. The time course of these changes deserves special attention since the beneficial changes accumulated within the first days and weeks and reached a stable level afterwards. A similar tendency of haemodynamic

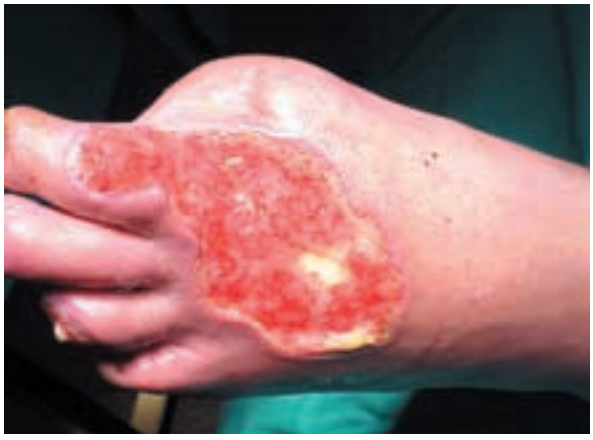

Figure 10. SS at baseline

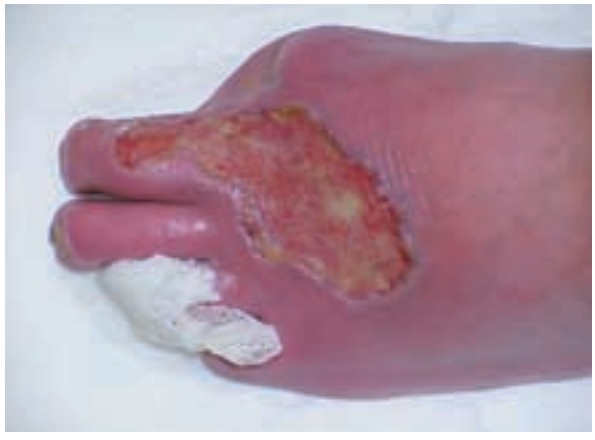

Figure 11. SS after 6 months

parameters was reported by the TACT trial authors [17], with most changes occurring within four weeks following the procedure. The influence of the procedure on the collateral circulation seems to be limited to a relatively short period of time just after the transplantation. The question remains as to whether repeated application of the treatment would bring better results. The survival rate of the affected legs in our group has been 70% so far.

Based on angiograms we failed to find any correlation between favourable clinical and angiographic effects of the treatment with respect to the large vessels. A trustworthy and objective method of evaluating vascular changes is still unavailable. The previously reported lack of a correlation between angiograms and clinical status is confirmed by our observations. Digital angiographic techniques including time-flow analysis and vasculature structural changes over the time analysis might provide a solution. Preliminary reports on such techniques indicate that in the future they may become precise diagnostic tools capable of monitoring clinical effects of angiogenesis stimulation [22].

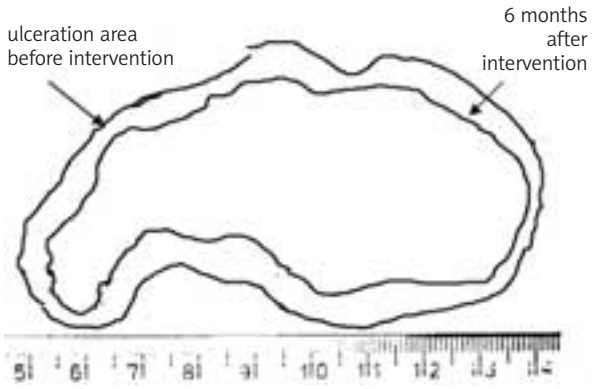

Figure 12. SS ulceration area changes

Scintigraphy seems to be another useful tool in the assessment of changes in the peripheral circulation. The results of the radionuclide studies correlated with clinical recovery and decline in a few cases.

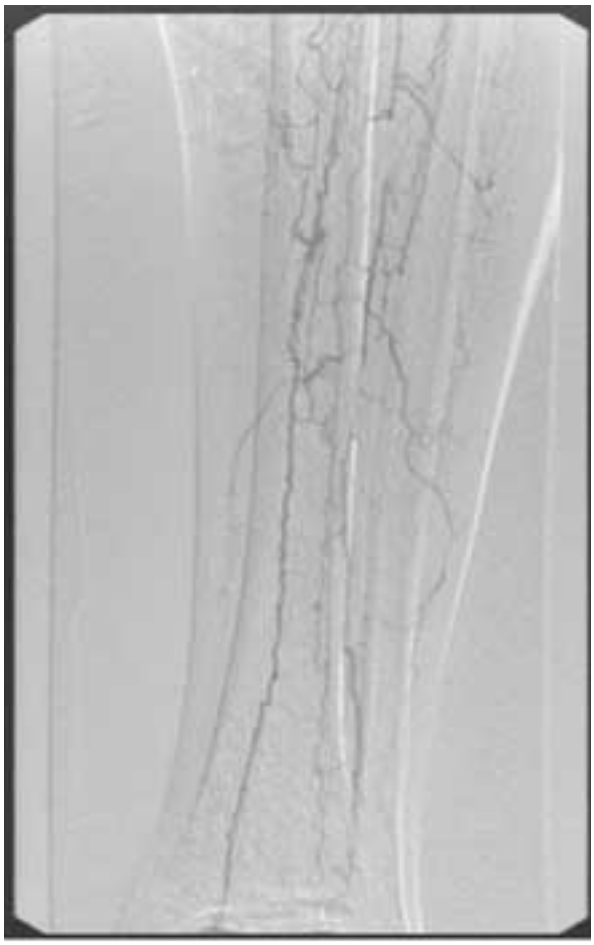

Figure 13. KB at base line

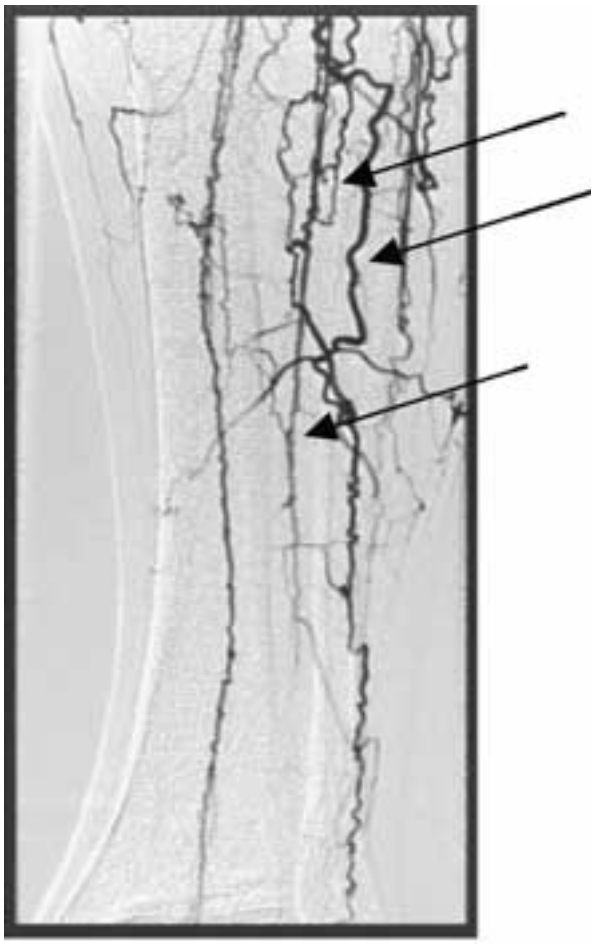

Figure 14. KB at 3 months

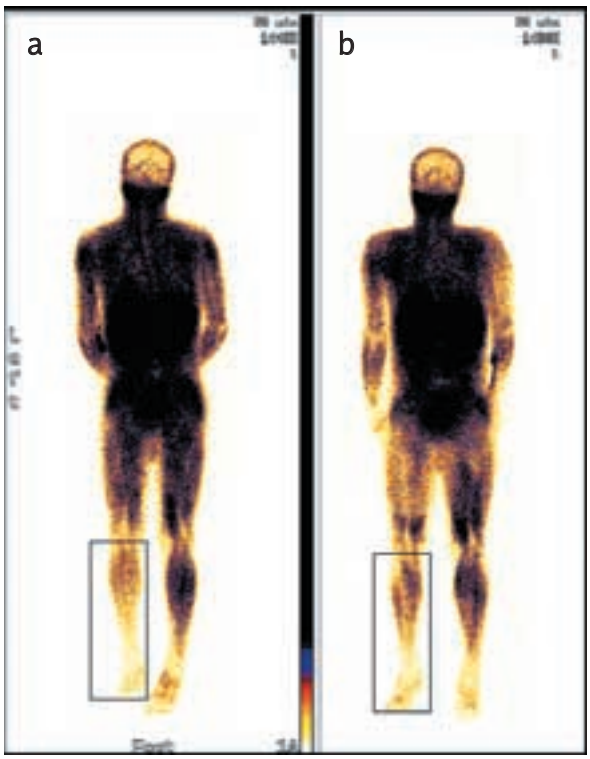

Figure 15. KB a) at base line, b) at 3 months

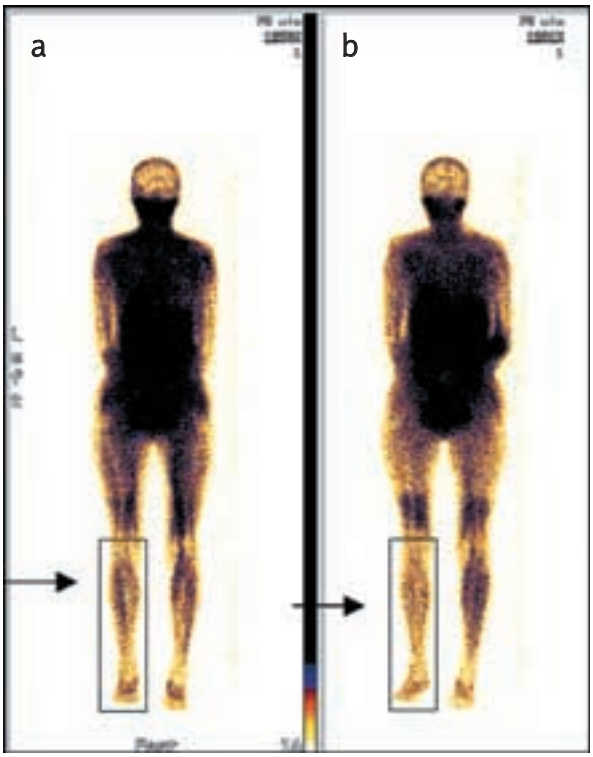

Figure 16. AJ a) at base line, b) at 3 months

Although cytology analysis did not show any correlation between the amount of mononuclears or CD34 cells transplanted and clinical outcome, such a relation cannot be excluded due to the small number of patients included in the study.

Preclinical studies suggest that the main mechanism of perfusion recovery in chronic ischaemic disease may be remodelling of the existing small vessels initiated by a stimulus provided by marrow transplants rich in cytokines and stem cells rather than neovascularisation [6, 23].

Conclusions

Our observations, consistent with the results from the Japanese group, suggest that transplantation of stem cells as well as other bone marrow components may lead to either small vessel vasculature recomposition or neovascularisation in advanced leg ischaemia. Randomised double-blind studies are needed to establish whether marrow stem cell transplantation will improve perfusion in critical limb ischaemia and whether the clinical outcome would depend on the marrow preparation mode and cellular content.

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Leczenie zaawansowanego niedokrwienia kończyn autologicznym przeszczepem komórek szpikowych

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Streszczenie

Wstęp: Leczenie chorych na krytyczne niedokrwienie kończyn napotyka na zasadnicze trudności. Nierzadko jedynym rozwiązaniem jest amputacja. W 2002 r. wyniki badań Tateishi-Yuyamy et al. wskazały na przeszczep komórek szpiku jako na potencjalnie nową terapię.

Cel. Ocena skuteczności autologicznej transplantacji szpiku kostnego w leczeniu chorych na krytyczne niedokrwienie kończyn.

Metodyka: Grupę badaną stanowiło10 chorych na krytyczne niedokrwienie w stadium Fontaine IV, którzy byli bez powodzenia leczeni metodami konwencjonalnymi i nie wymagali pilnej amputacji. Pobrany z talerza biodrowego szpik kostny zagęszczano separatorem. Uzyskany preparat podawano do niedokrwionej kończyny poprzez wielokrotne iniekcje domięśniowe w obszar stopy i podudzia. Ogólną liczbę komórek CD34 i AC133 pozytywnych w populacji komórek jednojądrzastych oceniono za pomocą cytometrii przepływowej. Po dwóch tygodniach oraz 1, 3, 6 i 12 miesiącach obserwacji oceniono następujące parametry: laser Doppler flux, przezskórne ciśnienie parcjalne tlenu, wskaźnik kostka/ramię, poziom odczuwanego bólu, zapotrzebowanie na leki przeciwbólowe, powierzchnię owrzodzenia, a także wykonano badanie angiograficzne i scyntygrafię podudzia.

Wyniki: Stwierdzono poprawę wartości wskaźnika kostka/ramię, przepływu skórnego w pomiarze laser Doppler flux oraz przezskórnego ciśnienia parcjalnego tlenu. W większości przypadków notowano zmniejszenie dolegliwości bólowych. U trzech pacjentów leczenie zakończyło się niepowodzeniem i amputacją kończyny. Nie stwierdzono żadnych efektów ubocznych leczenia. Brak było korelacji pomiędzy ilością podanych komórek a uzyskanym efektem klinicznym.

Wnioski: Autologiczny przeszczep komórek szpiku do objętej niedokrwieniem kończyny wydaje się potencjalnie skuteczną metodą poprawy krążenia obwodowego. Mechanizm obserwowanej poprawy wymaga dalszych badań.

Słowa kluczowe: angiogeneza, krytyczne niedokrwienie kończyn, miażdżyca zarostowa tętnic, komórki macierzyste szpiku

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