Long-term follow-up of patients with Buerger's disease after autologous stem cell therapy

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Abstract

Objective: We investigated the long-term results of autologous bone marrow mononuclear cells (ABMMNCs) implantation in patients with Buerger's disease (BD).

Methods: Twenty-eight patients (25 males and 3 females) who had BD and critical unilateral limb ischemia were investigated between April 2003 and August 2005. The patients were administered multiple injections of CD34+ and CD45+ positive ABMMNCs into the gastrocnemius muscle, the intermetatarsal region, and the dorsum of the foot (n=26) or forearm (n=2) and saline injection into the contralateral limb.

Results: The mean follow-up time was 139.6±10.5 months. No complication related to stem cell therapy was observed during the follow-up. The ankle–brachial pressure index evaluated at 6 months and 120 months was compared to the baseline scores (p<0.001 and p=0.021, respectively). Digital subtraction angiography (DSA) was performed for all patients at baseline, 6 months, and 120 months. The angiographic improvement was 78.5% and 57.1% at 6 and 120 months, respectively. Patients demonstrated a significant improvement in the quality of life parameters at 6 months compared to baseline (p=0.008) and 120 months compared to the baseline (p=0.009). The 10-year amputation-free rate was 96% (95% CI=0.71-1) in ABMMNC-implanted limbs and 93% (95% CI=0.33–0.94) in saline-injected limbs (p=1).

Conclusion: Autologous stem cell therapy could be an alternative therapeutic method for BD at long-term follow-up. *(Anatol J Cardiol 2019; 21: 00-00)*

Keywords: Buerger's disease, stem cell therapy, autologous bone marrow mononuclear cell

Introduction

Buerger's disease (BD) is a non-atherosclerotic, progressive vasculitis of the small and medium arteries. As there is a distally localized diffuse segmental involvement, revascularization is not frequently feasible. Instead, therapeutic angiogenesis by cellular strategies may be an option for patients with BD (1).

It has been reported that stem cell therapy leading to new collateral vessel development relieves ischemic symptoms in patients with BD (2-5). In contrast, previous studies have stated clinical limitations to stem cell therapy due to limited number of patients and short follow-up times (6).

In the first study on stem cell therapy that was published in 2002 by Tateishi-Yuyama et al. (6), 22 patients (44 limbs) with arteriosclerosis obliterans (ASO) were administered autologous bone marrow mononuclear cells (ABMMNCs). Further, it was reported that increased collateral vessel formation developed in ischemic limbs 6 months after implantation, and decrease in rest pain and increase in ankle-brachial pressure index (ABPI) and transcutaneous oxygen pressure were observed.

Furthermore, recent studies have shown that the implantation of ABMMNCs and autologous peripheral blood mononuclear cells (APBMNC) improve critical limb ischemia (CLI) (7-11).

In the present study, we aimed to evaluate the feasibility, safety, reproducibility, and efficacy of ABMMNC implantation in patients with CLI due to BD.

Methods

Study design

Twenty-eight patients were diagnosed with grade II or III BD between April 2003 and August 2005; according to the recom-

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Accepted Date: 10.12.2018 **Available Online Date:** 14.01.2019

DOI:10.14744/AnatolJCardiol.2018.12354

Anatol J Cardiol 2019; 21: 00-00
DOI:10.14744/AnatolJCardiol.2018.12354

mended classification by Rutherford et al. (12), none of the patients were suitable for conventional revascularization therapies. Informed written consent was obtained from all the patients, and the study was approved by our institution's Local Ethics Committee. The study protocol has been published previously and is also available with the full text of this article at https://www.jvascsurg.org/issue/S0741-5214(06)X0188-X. The 2-year results have also been published previously (3). The clinical characteristics of the patients are shown in Table 1.

Baseline evaluation

All patients underwent complete blood count; biochemical analysis, including liver and kidney functions, and fasting blood glucose; urine analysis; and serologic profile, including erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, rheumatoid factor, anticentromere antibody, antiphospholipid antibody, Scl-70, fibrinogen, complement measurements, serum homocysteine, and hypercoagulability screen (protein C, protein S, and antithrombin III plasma levels, factor V Leiden, and prothrombin 20210A gene mutation analysis); chest radiograph; electrocardiogram; transthoracic echocardiography; and ophthalmologic examinations. All patients also underwent a routine preharvest examination by an experienced hematologist from the Stem Cell Transplantation Unit. For patients who used aspirin and clopidogrel, medication was discontinued 5–7 days before ABMMNCs administration.

Standard vascular examination, including ankle–brachial pressure index (ABPI) measurement was assessed using duplex ultrasonography.

All patients underwent a validated progressive treadmill protocol with reduced initial speed (1.6 km/h); patients continued walking until they felt claudication pain or any other clinical condition that required the test to stop (13). The claudication onset time, claudication distance, and peak walking time and distance were recorded. Patients who were previously amputated below their knee were asked to walk with prosthesis for an increasing distance at a self-selected velocity. A 10-cm visual analog scale (VAS) was recorded monthly by the patients for both the ischemic and control limbs, where a score of 0 implied no pain and a score of 10 implied most severe pain ever experienced.

Systemic antibiotic therapy was prescribed for patients with trophic ulcers that were determined using microbiologic quantitative tissue cultures and sensitivity results. Digital color photography was used for the documentation of ischemic ulcers. All patients underwent local wound care and surgical debridement until three cultures revealed negative microbiologic results. Thereafter, the patients were accepted for cellular therapy administration.

Intra-arterial digital subtraction angiography

Digital subtraction angiography (DSA) (Multistar Plus/ T.O.P., Siemens AG, Forchheim, Germany) of both upper and lower extremities was performed for all patients at baseline, 6 months, and 120 months of follow-up. The amount and the force of low-osmolality nonionic contrast injection and the position of the catheter tip (5F, Weinberg, pigtail, Digiflex, Boston Scientific Corp, Watertown, Mass) was strictly fixed for DSA studies to obtain identical imaging conditions.

Angiographic mapping of both lower limbs and comparison of all the evaluated segments were reviewed by two independent radiologists blinded to the treated extremity. The angiographic scores for the formation of new collateral vessel formation were assessed as 0 (no collateral development), 1 (slight), 2 (moderate), and 3 (rich), as described previously.

Vascular Quality of Life Questionnaire

The King's College Hospital Vascular Quality of Life Questionnaire (VascuQol) was used to assess quality of life (QoL) at baseline and 3, 6, and 120 months after the procedure (14). The 25-item questionnaire included parameters to investigate pain and other symptoms as well as patient's activity and social and emotional status. The total VascuQol score was between 1 and 7 (all item scores were divided by 25) for each evaluation.

Bone marrow harvest and isolation of mononuclear cells

After the patients were stabilized in a prone position, the stem cell transplantation team collected the bone marrow from bilateral spina iliaca posterior superior under general anesthesia, and this procedure was completed approximately 2 hours before the ABMMNCs were implanted. The collected bone marrow (mean amount, 653.2±77.3 mL) was immediately transferred to the Apheresis Unit. During the implantation process, a total mononuclear cell amount of 1±10e8–9/mL was targeted and unnecessary red blood cell (RBC) implantation and higher harvest volumes were avoided. The harvest material was processed on COBE® Spectra (Gambro BCT, Lakewood, Colo) using the bone marrow processing program and software version 5.1.

After the RBCs were depleted and the total volume was reduced using a continuous flow cell separator in a closed system (15), 91%±2% RBC depletion was achieved and ABMMNCs and total mononuclear cells were concentrated to a final volume of 59.9±9.2 mL and 1.69±0.89 ±10e9/mL, respectively. The total number of implanted CD34+ cells was 53.1±35.9 ±10e6. A cytofluorometric analysis showed that 99% of implanted stem cells were viable and 97.5%±2.2% of CD45+ cells were included. Cultures of cell preparations were negative for bacterial and fungal contamination.

ABMMNCs Implantation

The implantation of ABMMNCs was performed within 2 hours after bone marrow was collected, and multiple intramuscular injections were administered into the gastrocnemius muscle, intermetatarsal region of the limb with CLI, and around the trophic lesions. The implantation of ABMMNCs started 4–5 cm proximal to the obstructive lesion and continued distally. A 22-gage spinal needle and a 7-cm grid were used to implant approximately 1 mL of ABMMNCs into each injection site (3–4 cm deep and oblique) for a median total of 54±7 sites (range, 41–70). For patients who

required debridement of ischemic ulcers, general anesthesia was performed, whereas mild sedation was preferred for other patients. During each implantation, saline solution was also injected into the contralateral limb in eligible patients.

Follow-up

Patients were seen in the outpatient department at 1 month, 3 months, 6 months, and thereafter annually for postoperative evaluation.

Short-term follow-up

The clinical operative and follow-up data were prospectively recorded in a computerized database. Three (10.7%) patients were on anti-lipid drugs at their initial evaluation in the outpatient clinic (Table 1). Aspirin (300 mg/day), statin (in case of total cholesterol >150 mg/dL), and L-arginine (500 mg/day) were started in all patients at the first visit, and patients were required to take this medication for 6 months prior to the study start.

The patients were examined in the outpatient clinic every 2 weeks postoperatively for trophic lesions and evaluated for pain scores and QoL using the VascuQol questionnaire. DSA was performed every 6 months.

Long-term follow-up

All patients were called after 10 years and were evaluated for ABPI and VascuQol scores as well as whether they had amputation. Twelve (42.8%) patients maintained strict smoking cessations for at least 10 years; 15 (53.5%) patients were taking aspirin/clopidogrel, and 13 (46.5%) patients were taking cilostazol with aspirin/clopidogrel. DSA was performed every 120 months.

End points

The primary end points were total healing of the most prominent lesion while avoiding major or minor amputation, the relief of rest pain without the need for analgesics, and the safety and feasibility of the treatment. Secondary end points were the alterations in the ABPI, angiographic evidence of collateral vessel formation or remodeling, QoL, and amputation-free survival.

Statistical analysis

Because of the small sample size and abnormal distribution of the variables, non-parametric tests were used to measure the difference. We used the Friedman's test to calculate the difference between the groups and the Wilcoxon signed-rank test to determine which group created this difference. The Bonferroni adjustment was also used for the significance level. The amputation-free rate was calculated using the Kaplan–Meier method. The 95% confidence interval (CI) was calculated for each test. Data were analyzed using The Statistical Package for Social Sciences (SPSS) version 22.0 (SPSS Inc, Chicago, Illinois, USA) for Windows (Microsoft Corp, Redmond, Washington, USA). A two-tailed p value of <0.05 was considered statistically significant.

Table 1. Demographic characteristics of the study group

Variable	n	%
Mean age (years, mean ± SD)	42.6±7.9 (25-56)	
Male	25	89.2
Duration between diagnosis and ABMMNCs implantation (years mean±SD) (range)	9.5±4.8 (1-23)	
Hypertension	3	10.7
Hyperlipidemia	3	10.7
Previous smoking	28	100
History of intermittent claudication	26	92.8
Pain at rest (narcotic requirement)	23	82.1
Ischemic non-healing ulcer	18	64.3
Thrombophlebitis	18	64.3
Raynaud's phenomenon	11	39.2
Sensorial findings	21	75
Abnormal Allen's test result	14	50
Upper extremity involvement by DSA	9	32.1
Previous ethanol abuse	8	28.6
Previous hyperbaric oxygen	13	46.4
Previous sympathectomy	17	60.7
Previous sympathetic nerve block	9	32.1
Previous amputation	12	42.8
Major/minor	2/10	7.1/35.7
Distal bypass graft	2	7.1
Below knee/crural arteries	1/1	3.6/3.6
Previous infusion of iloprost	5	17.8
Medications		
ACE-inhibitor/ARB	1	3.6
Statin	3	10.7
ASA/clopidogrel	22	78.6
Pentoxifylline	26	92.8
Calcium channel blocker	19	67.8
Cilostazol	1	3.6
NSAID	20	71.4
Morphine	14	50

Data presented as n (%) or mean±SD. ABMMNCs - autologous bone marrow mononuclear cells; DSA - digital subtraction angiography; ACE - angiotensin converting enzyme; ARB - angiotensin receptor blocker; ASA - acetylsalicylic acid; NSAID - nonsteroidal anti-inflammatory drug; SD - standard deviation

Results

The ratio of patients diagnosed with BD to those with ASO has been 1:4 at our outpatient clinic since the year 2000. During this study period, 52 patients with BD (46 males and 6 females) were admitted to the Heart Center at Ankara University. Thirty-two pa-

Anatol J Cardiol 2019; 21: 00-00
DOI:10.14744/AnatolJCardiol.2018.12354

tients were Rutherford grade II-III, and 28 patients were included in the present study (Fig. 1).

Twenty patients who were Rutherford grade I disease were excluded. Four patients were not included in the study, as they refused to undergo cellular therapy after they received detailed information about the possible side effects. All patients had a history of smoking and applied with ischemic rest pain and/or trophic lesions. The mean age at disease onset was 33 years (range, 20–45 years), whereas the mean age at initial evaluation was 42 years (range, 25–54 years). The infrapopliteal artery and upper extremities were involved in 28 (100%) and 9 patients (32%), respectively (Table 1).

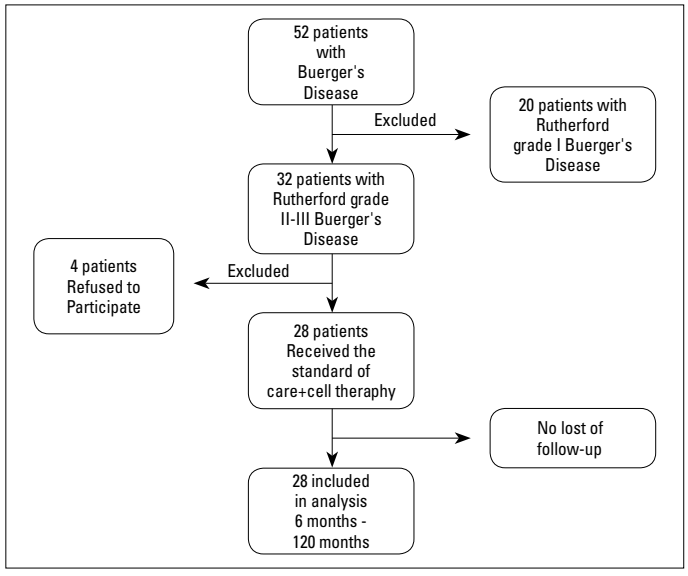

Figure 1. Study diagram showing the flow of participants through each stage

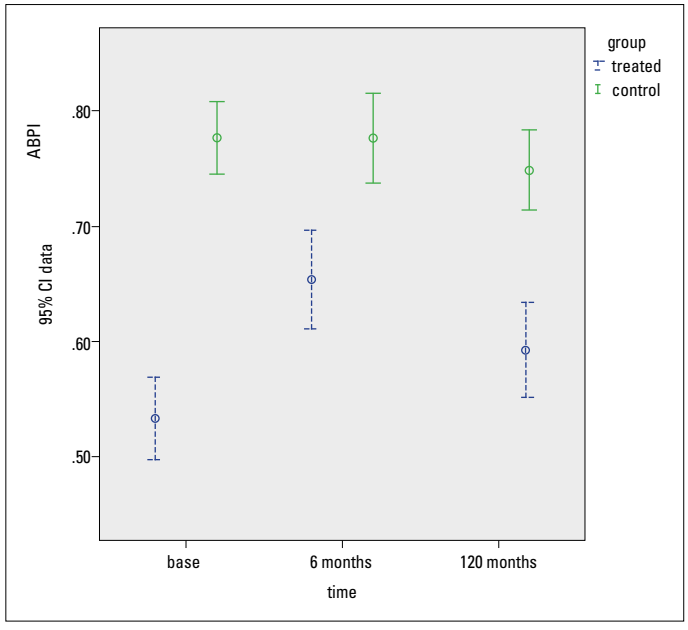

Figure 2. Resting ankle–brachial pressure index (ABPI) was measured three times in the treated and control groups (mean±standard deviation, 95% confidence interval data). Autologous bone marrow-mononuclear cell (ABMMNC) implanted limbs and saline-injected contralateral limbs at baseline and 6 and 120 months after the procedure

Procedural data

The same surgical team performed all procedures. The mean duration for total bone marrow harvest was 35.7±6.1 min (range, 27–50 min) and the mean duration for ABMMNCs implantation was 32.5±4.4 min (range, 22–39 min). Approximately 2 million cells were implanted in a volume of 1 mL during each injection. To eradicate necrotic and devitalized tissues, surgical debridement was performed in 18 patients (64.2%) who had ischemic ulcers.

Safety data

No complications due to ABMMNCs implantation occurred. A blood transfusion was performed following a bone marrow harvest; three (10.7%) patients were diagnosed with iron deficiency anemia and were treated with oral iron replacement therapy for 3 months. All patients who had rest pain were hospitalized and discharged on the second day according to the protocol. The duration of hospitalization after ABMMNCs implantation was 26.4±14.6 days (range, 7–52 days) for patients with trophic lesions. No patient had retinopathy or teratoma in funduscopic examinations. The levels of C-reactive protein, white blood cells, and fibrinogen at baseline and follow-up were similar.

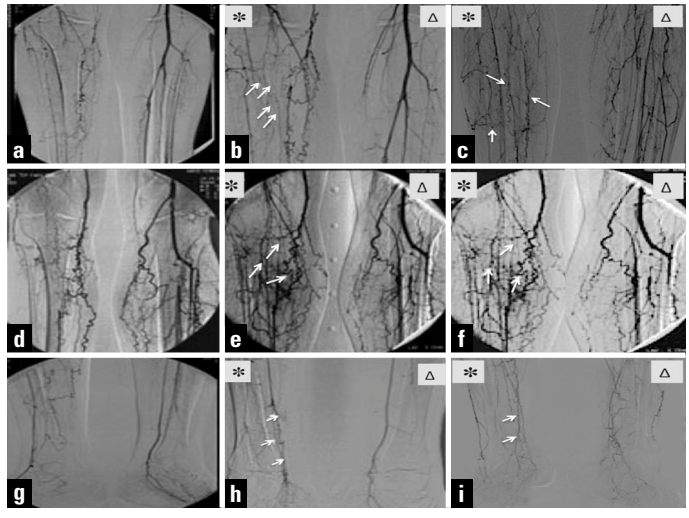

Figure 3. Pre and postoperative angiograms of the lower extremities. (a, d, g) The baseline digital subtraction angiographic (DSA) studies. (b, e, h) Lower extremity DSA study confirms new collateral vessel formation in the right limb at the 6 month follow-up after the implantation of autologous bone marrow-derived mononuclear cells (ABMMNC). (c, f, i) Lower extremity DSA study confirms new collateral vessel formation in the right limb at the 120-month follow-up after implantation of autologous bone marrow mononuclear cells.
*ABMMNC-implanted limb.
$^{\Delta}$Saline-injected control limb.
Arrows indicate new collateral vessel formations that were visible at ABMMNC injection sites compared with the baseline angiography

Follow-up evaluation

No patient was lost to follow-up, and the mean follow-up duration after ABMMNCs implantation was 139.6±10.5 months.

Ankle–brachial pressure index

The ABPI increased from 0.52±0.09 at the baseline to 0.67±0.13 after 6 months (p<0.001) and to 0.58±0.10 after 120 months (p=0.021) of follow-up (Fig. 2). However, ABPI did not change significantly at 6 and 120 months in the contralateral saline-injected leg.

Digital subtraction angiography

New vessel formation was observed in 22 (78.5%) patients at 6 months and 16 (57.1%) patients at 120 months (Fig. 3).

Quality of life

The VascuQol scores showed significant improvement in QoL at 6 months after ABMMNC implantation (p=0.008) and further improvement was achieved at 120 months (p=0.009). Additional subgroup analyzes for activity, pain, and other symptoms as well as emotional and social items are presented in Figure 4.

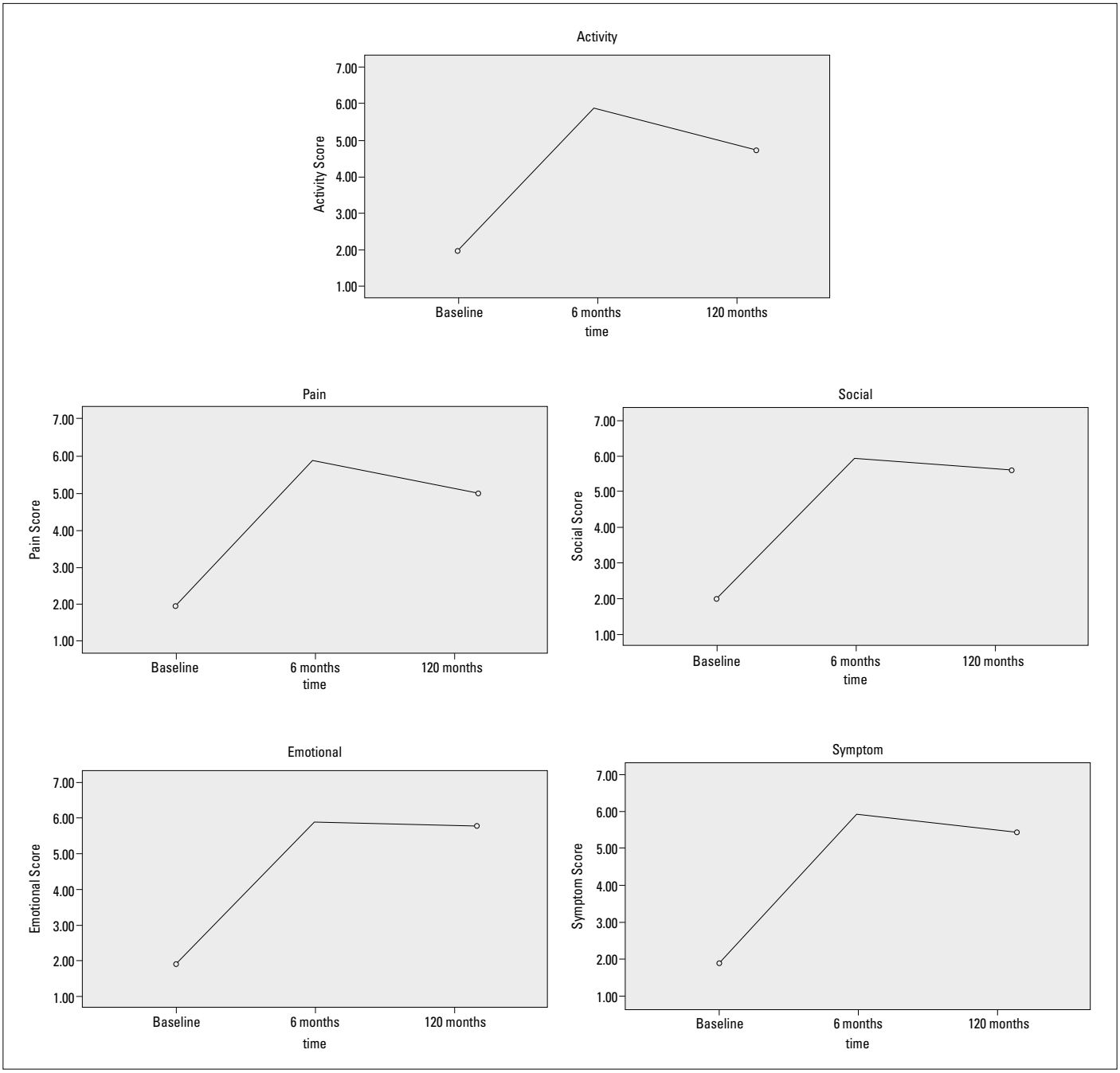

Figure 4. Vascular Quality of Life Questionnaire (VascuQol) subgroup values at baseline change from 6 months and at 6 months change from 120 months of follow-up (mean±standard deviation)

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DOI:10.14744/AnatolJCardiol.2018.12354

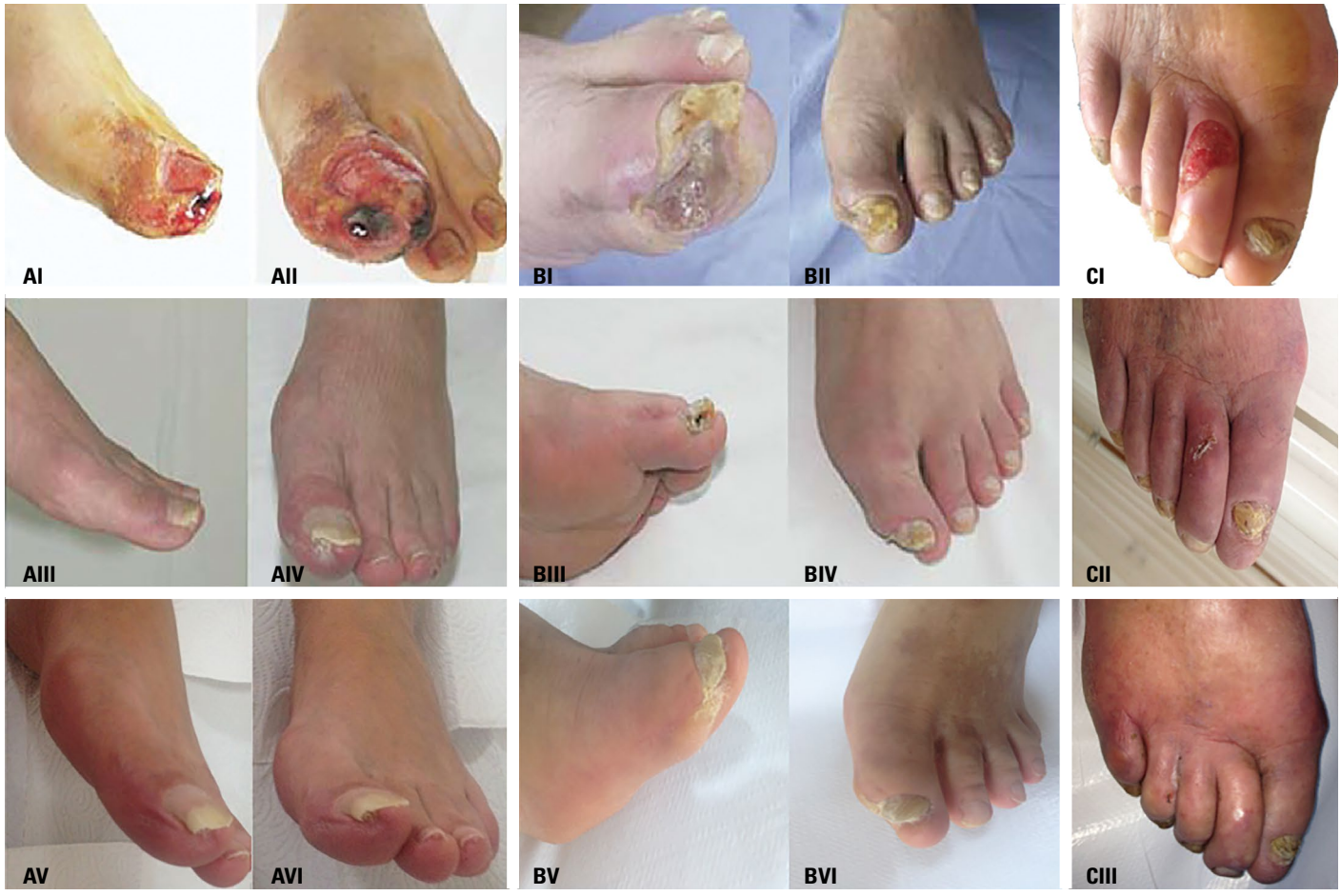

Figure 5. The preoperative (AI, AII–BI, BII–CI) and postoperative (AIII, AIV–BIII, BIV–CII) images. AI-AII, CI Non-healing ischemic ulceration on the great toe after surgical debridement. AIII, AIV–BIII, BIV–CII Complete wound healing after 24 months of ABMMNC implantation. AV, AVI–BV, BVI, and CIII Perfect healing trophic lesion and nail fold after 120 months

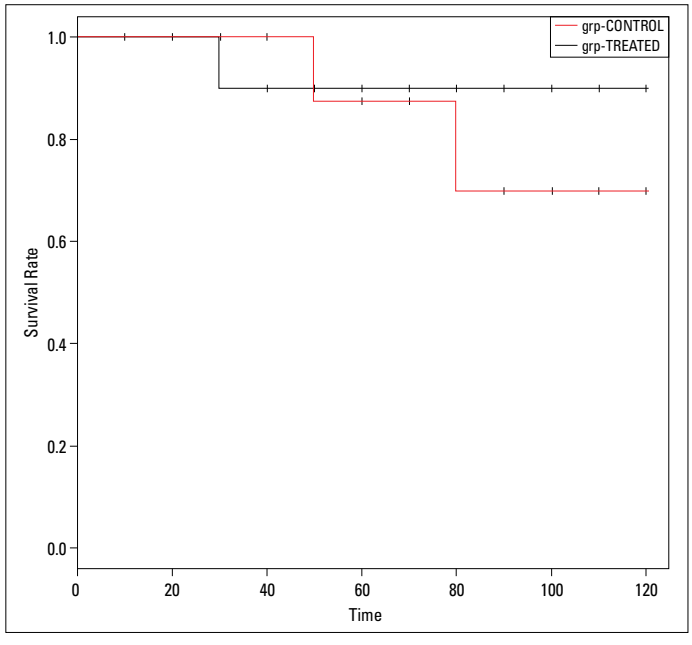

Figure 6. Amputation-free survival rate of treated [ABMMNC limbs 96% (95% CI 0.71–1)] and control [saline limbs 93% (95% CI 0.33–0.94)] groups. Probability of amputation was determined using the Kaplan–Meier curve

Ulcer status

Ischemic ulcers healed completely in 17 patients (94%) after 120 months; especially, three patients had perfect healing after 10 years (Fig. 5).

Amputation rate and survival

One patient in the ABMMNCs implantation arm and 2 patients in the saline injection arm had toe amputation; however, the difference was not statistically significant (p=1) (Fig. 6). Patients had a history of smoking.

A 62-year-old male patient was diagnosed with Alzheimer disease 9 years after stem cell therapy. This patient consulted to a neurology department.

Discussion

Stem cell therapy has been recently performed in patients with BD and ASO. This procedure that aims the development of new vessels has gained popularity during the last 10 years. In 2002, Tateishi–Yuyama et al. (6) implanted stem cells from a pa-

tient's bone marrow to his ischemic leg and reported new collateral development on angiography after 6 months, and rest pain and the duration of maximum walking improved in patients at the 24-month follow-up.

In 2005, Ishida et al. (4) performed peripheral autologous stem cell transplant on patients with peripheral arterial disease (PAD) and observed decreased ischemia. In the first part of the present study published in 2006, we injected CD34+ and CD45+ positive ABMMNCs that were obtained from the bone marrow of patients with BD into their legs, and we showed the development of new vessel formation during a mean follow-up of 16.6 months (3).

In previous studies, it has been shown that autologous bone marrow stem cell transplant decreased the rate of amputation in patients with CLI (16, 17). No significant difference was found between the effect of treatments with bone marrow mononuclear cells and granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood mononuclear cells on long term morbidity (amputation) and mortality in patients with CLI (18). In this study, it was emphasized that CD34+ cells were important indicators for vascular therapy.

Smoking and tobacco consumption are major factors associated with the development of BD; since tobacco may trigger an immune response or unmask a clotting defect, tobacco can incite an inflammatory reaction in the vessel wall (19). Also, lower extremity exercise training contributes to improve maximum walking time, peak oxygen uptake, and QoL in patients with intermittent claudication (20). Guo et al. (21) reported that modest clinical improvements in patients who stop smoking but are not treated with ABMMNCs might not cure ischemia alone but that smoking cessation is a critical factor in providing appropriate stem cell function. In our study, we have seen the long-term positive effects of ABMMNCs treatment.

A significant decrease in the amputation rate was detected in patients with BD following autologous bone marrow stem cell CD34+ and CD133+ therapy (22). The effects of mesenchymal and embryonic stem cells on the beginning of angiogenesis are also a popular issue (23, 24).

Treatment with in vitro-expanded, peripheral blood-derived, autologous stem cells was found efficient and safe in patients with ASO at the long-term follow-up (25, 26).

In a meta-analysis by Wang et al. (27), the randomized and nonrandomized studies on ABMMNCs implantation in patients with PAD were evaluated, and it was reported that cell therapy is advantageous in patients with no scope for revascularization.

In the present study, we evaluated patients with BD with a mean follow-up time of 139.6 months. We observed that a significant increase in ABPI continued in the legs implanted with ABMMNCs. However, there was a significant decrease in the legs injected saline solution. When the QoL was evaluated, we observed that improvement in activity, pain, other symptoms, and social and emotional parameters also continued. The amputation rate was higher in the control group without significant difference.

Study limitation

The major limitation of this study is the small number of patients.

Conclusion

The present study in which we reported our long-term results shows that ABMMNCs implantation did not cause possible side effects, such as out-of-control cell reproduction, intra-arterial occlusion, and dysrhythmia in patients with BD. After a 10-year follow-up, we can say that the cell therapy procedure is safe. We observed that ischemic ulcer wounds in patients healed completely, and patients had better QoL during the follow-up.

Larger and randomized series of stem cell therapy studies together with new cellular modalities are needed particularly in patients with BD and PAD.

Funding: This work was supported Biotechnology Institute Research Fund and Ankara University School of Medicine Research Council, Turkey (EA-TUBA-GEBIP/2004-1-1).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Ç.B., S.D., E.Ö., R.A.; Design – Ç.B., S.D., M.Ç., M.Ş., R.A.; Supervision – Ç.B., S.D., E.Ö., B.İ., R.A.; Materials – Ç.B., S.D., E.Ö., M.Ç., R.A.; Data collection &/or processing – Ç.B., S.D., E.Ö., M.Ç.; Analysis &/or interpretation – Ç.B., M.Ç., A.İ.H., R.A.; Literature search – Ç.B., S.D., M.Ç., A.İ.H.; Writing – Ç.B., S.D., A.İ.H., B.İ., R.A.; Critical review – Ç.B., S.D., M.Ş., R.A.

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