Eur J Vasc Endovasc Surg **34**, 424–431 (2007)
doi:10.1016/j.ejvs.2007.04.005, available online at http://www.sciencedirect.com on ScienceDirect

Cold-stored Venous Allografts in the Treatment of Critical Limb Ischaemia

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Objectives. *To assess the outcome of cold-stored venous allografts in critically ischemic limbs in patients with no ipsilateral autogenous greater saphenous vein.*
Design. *A non-randomised, retrospective, single-center study.*
Methods. *From September 2000 to June 2006, 46 cold-stored venous allografts obtained during multiorgan harvest were implanted into 44 critically ischaemic limbs of 43 patients. The indication for reconstructions was rest pain (24%) or tissue lost (76%). Sixty-seven percent of procedures were performed as secondary reconstructions, and 61% of veins were anastomosed to tibial or pedal arteries. Thirty-seven percent of patients received prednisone, and 46% tacrolimus as postoperative immunosuppressive therapy. Mean patient follow-up period was 13.3 months (range 1 week to 60 months).*
Results. *The secondary patency rate for the cohort was 83 ± 5.6% at 1 month, 64 ± 8.2% at 6 months, 57 ± 10.0% at 12 months and 46 ± 10.7% at 24 months. Limb salvage rate was 96 ± 3.1% at 1 month, 78 ± 6.9% at 6 months, 71 ± 8.1% at 12 months and 50 ± 11.8% at 24 months.*
Conclusion. *Cold-stored venous allografts are an alternative conduit for limb salvage procedures when ipsilateral autogenous vein is unavailable.*

Keywords: Venous allografts; Critical ischaemia; Limb salvage.

Introduction

A good-quality autologous vein provides the best results for infra-inguinal bypass.[1] In a considerable group of patients with critical ischaemia, the greater saphenous vein is not available for vascular reconstruction.[2–4] The use of a prosthetic graft in the field of chronic leg ulcerations is accompanied with a high risk of infection.[5]

In such circumstances, alternative autogenous conduits such as an arm vein,[6] lesser saphenous vein[7] or composite autogenous vein[8] are used. In addition, allogenous materials such as cryopreserved venous allografts,[9] cold-stored venous allografts,[10] cryopreserved arterial allografts,[11] cold-stored arterial allografts,[12] umbilical cord vein allografts[13] or Ovine collagen biografts[14] are available to use as conduits.

However, arterial as well as venous allografts are antigenic and the process of chronic rejection is a limiting factor in long-term patency rates of these by-pass conduits.

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At our Institute, the Vascular Surgery Unit is integrated closely with the Transplant Center, so it is possible to obtain allogenic blood vessels for vascular reconstruction during regular multi-organ harvests.[15] Over the past six years we have used cold-stored venous allografts in patients with no suitable ipsilateral greater saphenous veins and critically ischemic limbs. This present paper reports our results.

Material and Methods

The work was approved by the Ethical Committee of the Institute for Clinical and Experimental Medicine in Prague. The work is a retrospective study dealing with the critically ischaemic lower limbs treated by cold-stored venous allograft reconstructions. Ipsilateral autogenous greater saphenous vein was unavailable in all patients.

Patient population

From September 2000 to June 2006, 46 cold-stored venous allografts were implanted into 44 critically ischaemic limbs of 43 patients (men 21, women 22). Mean patient age at primary graft implantation was

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66.8 years (range 46 to 85 years). Demographic data for all 43 patients are shown in Table 1.

The indication for the 46 reconstructions was either rest pain ($n = 11$, 24%) or tissue lost ($n = 35$, 76%). Suitable ipsilateral autogenous greater saphenous vein was not available in these patients. The most frequent reason for lack of ipsilateral vein was it's use as conduit for a prior leg bypass (43%) (Table 2). Sixty-seven percent of 46 cold-stored venous allograft reconstructions were secondary or even tertiary procedures, performed after a previous failed infrainguinal reconstruction. In 59 percent of venous allograft reconstructions, there was no contralateral autogenous greater saphenous vein available, mainly because of it's previous harvest (20%) (Table 2). In the remaining 41 percent of patients with a suitable contralateral vein we elected not to utilise this because of the high risk that it would be required for future intervention in that leg.[16]

All patients underwent preoperative arteriography. The quality of the peripheral outflow tract distal to the graft was outlined by using Rutherford's run-off-index.[17] The mean value of the index for the 46 reconstructions was 4.9 (range 2 to 8, SD $\pm$ 1.8).

Harvest and preservation of venous grafts

All venous allografts (greater saphenous veins) were obtained from donors with the diagnosis of brain death in the course of a multiorgan harvest. The mean age of the donors was 32 years (range 17 to 54 years).

After removal, the venous grafts were flushed with heparinised conservation solutions commonly used in multiorgan harvests, i.e. Custodiol or University of Wisconsin. The grafts were stored at a temperature of about 4 degrees Centigrade using the same types of solutions as those used for flushing, with no additional antibiotics. The mean cold ischemic time of venous grafts was 5 days (range 5 hours to 13 days). The patients indicated for the use of venous allograft were integrated into a waiting list similar to that used for potential recipients in solid organ transplantation. The ABO compatibility, but no HLA compatibility, was maintained between donors and recipients of venous allografts. Similarly, no cross-match was performed. In all organ donors bacteriological and serological tests (for HIV, hepatitis C, hepatitis B, cytomegalovirus, syphilis, Epstein-Barr virus) were performed before the multiorgan harvest.

Table 1. Demographic data for 43 patients in whom cold-stored venous allografts were used

Characteristic	*N*	%
Diabetes	30	70
Tobacco use	20	47
Ischaemic heart disease	26	61

Table 2. Reasons of lack of suitable ipsilateral and contralateral autogenous saphenous veins in 46 reconstructions

Greater saphenous vein	Ipsilateral leg	Contralateral leg
Previously used for vascular reconstruction	20/46 43%	9/46 20%
Previously used for coronary reconstruction	7/46 15%	5/46 11%
Previously stripped	3/46 7%	4/46 10%
Poor quality determined by ultrasound vein mapping	5/46 11%	3/46 7%
Poor qualty determined during op revision	11/46 24%	1/46 2%
History of leg amputation	–	5/46 11%
Expected need for the vein in the future*	–	19/46 41%

* All patients with diabetes mellitus + coronary artery disease + age under 70 as published by Tarry *et al.*[16]

Characteristics of procedures

Characteristics of the operative procedures of the 46 venous allograft are shown in Table 3.

Immunosupressive and antithrombotic therapy

From September 2000 to September 2004 a variety of immunosuppresive protocols including prednisone, azathioprime, cyclosporine A were used in patients after the allovenous reconstructions (Table 4). Drug dosages and the duration of administration were not standardized. In September 2004, we started using an immunosuppressive protocol consisting of orally administered FK 506 (tacrolimus, Prograf®, Astellas Pharma Ltd.), with the drug blood level generally

Table 3. The sites of proximal and distal anastomosis of 46 venous allografts reconstructions

		No	%
Inflow artery	External iliac	2	4
	Common femoral	33	72
	Superficial femoral	4	9
	Popliteal, above knee	1	2
	Prosthesis, aortofemoral	2	4
	Prosthesis, ilicofemoral	3	7
	Prosthesis, femoropopliteal	1	2
Outflow artery	Popliteal, above knee	9	20
	Popliteal, below knee	9	20
	Tibial anterior	7	15
	Tibial posterior	11	23
	Peroneal	7	15
	Pedal	3	7

Table 4. Type of immunosuppression in 46 venous allografts reconstructions

Immunosuppressive protocol	*N*	%
No immunosuppression	5	11
Prednisone	17	37
Azathioprime	1	2
Cyclosporine A	2	4
Tacrolimus	21	46

ranging between 4 and 7 ng/ml. Tacrolimus was administered throughout the entire period of allograft patency and blood levels were determined periodically. This type of immunosuppression was used in 21 (46%) patients (Table 4).

Anticoagulants and antithrombotic drugs

The drugs used postoperatively to influence blood coagulation as of the date of discharge are summarised in Table 5.

Follow up periods

We defined three follow up periods, namely for the patient, for the limb, and for the vascular procedure. Each of them started on the day of the operation. The death of the patient or the date when the patient was last known to be alive were the end points of the patient follow-up period. The follow-up period for the patency rate ended when the graft was confirmed to be occluded or last known to be patent. The graft patency was evaluated only by a vascular surgeon or diagnostic tests. The follow-up period for the limb salvage rate ended when a major limb amputation was done, the patient died, or the patient was last known to have an affected limb. A major limb amputation was defined as an amputation which was unable to preserve a sufficiently functional foot remnant to allow standing and walking without a prosthesis.[17]

Table 5. Antithrombotic drugs in 41 venous allografts reconstructions patent as of the date of dimission

	N	%
acetylsalicylic acid	15	37
ticlopidine	17	42
LMWH	3	7
warfarin	2	5
warfarin + acetylsalicylic acid	2	5
warfarin + ticlopidine	1	2
Clopidogrel + acetylsalicylic acid	1	2

LMWH, low molecular weight of heparin.

From September 2004 we employed along with the standard immunosuppressive protocol a standard protocol for duplex ultrasound surveillance of patients after the allovenous reconstructions. The patients were seen in three-monthly intervals to check the graft patency and the FK 506 blood levels as well. The patency of reconstructions was verified by clinical examinations as well as ultrasonography at identical time intervals. If signs of bypass stenosis were observed with duplex ultrasonography, angiography (conventional or computed) was performed.

Statistical analysis

Patient survival rates, graft patency rates, and limb salvage rates were determined by the Kaplan–Meier method. Differences between groups were tested for significance using Wilcoxon's signed rank test. Differences between groups were considered significant for P values less than 0.05.

Results

The mean patient follow-up period was 13.3 months (range 1 week to 60 months), the mean limb salvage follow-up period was 13.4 months (range 1 day to 58 months) and the mean graft patency rate follow-up period was 10 months (range 1 day to 56.5 months), respectively.

There were no deaths during the thirty-day perioperative period. The overall thirty-day morbidity was 24%. Systemic complications included acute GIT hemorrhage in 1 patient (2%). Local complications included wound infection (11%), wound hemorrhage without surgical intervention (4%), wound hemorrhage that necessitated surgical intervention (2%), vein allograft bypass rupture (2%), and graft thrombosis with limb amputation (2%). Patients survival rate was 100% at 1 month, $92 \pm 4.6\%$ at 3 months, $88 \pm 5.7\%$ at 6 months, $88 \pm 5.7\%$ at 12 months, $88 \pm 5.7\%$ at 24 months and $74 \pm 15.4\%$ at 36 months (Fig. 1).

The primary patency rate for the cohort was $83 \pm 5.6\%$ at 1 month, $70 \pm 7.1\%$ at 3 months, $47 \pm 8.3\%$ at 6 months, $35 \pm 9.4\%$ at 12 months, $31 \pm 9.0\%$ at 24 months and $15 \pm 8.1\%$ at 36 months (Fig. 2).

Six endovascular procedures (5 PTA, 1 PTA/stent) were needed to maintain the primary patency of venous allografts. The primary assisted patency rate for the cohort was $83 \pm 5.6\%$ at 1 month, $73 \pm 6.9\%$ at 3 months, $61 \pm 8.3\%$ at 6 months, $57 \pm 10.0\%$ at 12 months, $46 \pm 10.7\%$ at 24 months and $23 \pm 10.1\%$ at 36 months.

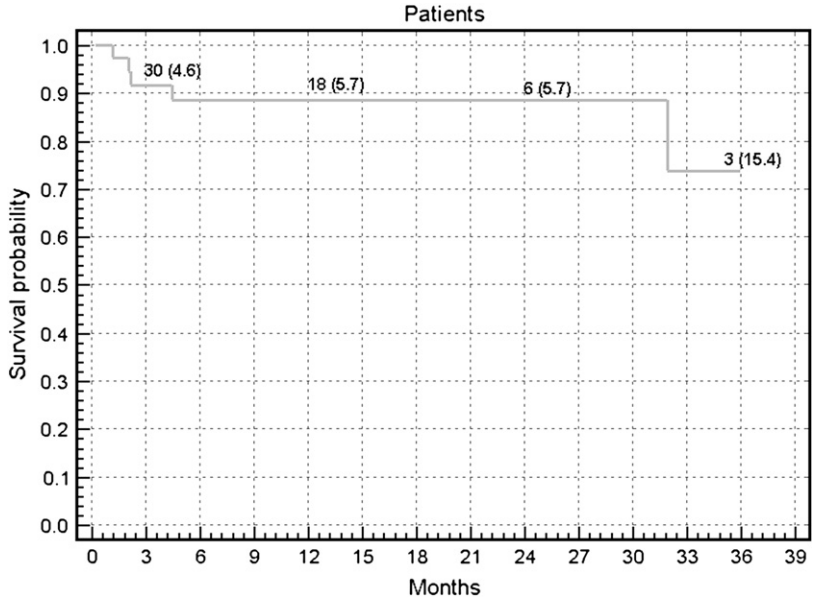

Fig. 1. Patients survival curve. Kaplan–Maier method. Number at rist (% SEM).

Six surgical thrombectomies and two local usages of tissue plasminogen activator were needed to maintain the secondary patency of venous allografts. The secondary patency rate for the cohort was $83 \pm 5.6\%$ at 1 month, $73 \pm 6.9\%$ at 3 months, $64 \pm 8.2\%$ at 6 months, $57\% \pm 10.0\%$ at 12 months, $46 \pm 10.7\%$ at 24 months and $31 \pm 11.4\%$ at 36 months (Fig. 3).

Limb salvage rate was $96 \pm 3.1\%$ at 1 month, $81 \pm 6.3\%$ at 3 months, $78 \pm 6.9\%$ at 6 months, $71 \pm 8.1\%$ at 12 months, $50 \pm 11.8\%$ at 24 months and $43 \pm 12.2\%$ at 36 months (Fig. 4).

To compare the influence of FK 506 immunosuppression, the cohort of patients was divided into a group with standard FK 506 immunosupression ($N = 21$) and one with other types or no immunosuppression ($N = 25$). The primary patency rate for the FK 506 group was $76 \pm 9.3\%$ at 1 month, $65 \pm 10.8\%$ at 3 months, $59 \pm 11.5\%$ at 6 months and $16 \pm 14.0\%$ at 12 months. The primary patency rate for the group of patients with other type or no immunosuppresion was $88 \pm 6.5\%$ at 1 month, $75 \pm 8.9\%$ at 3 months, $42 \pm 10.5\%$ at 6 months and $42 \pm 10.5\%$ at 12 months,

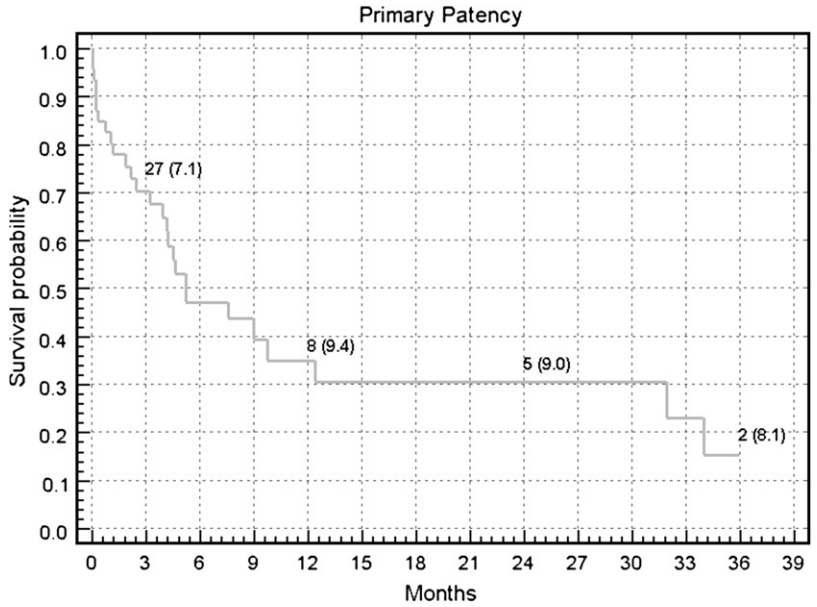

Fig. 2. Primary patency curve for 46 revascularizations procedures with cold-stored venous allografts. Kaplan–Maier method. Number at rist (% SEM).

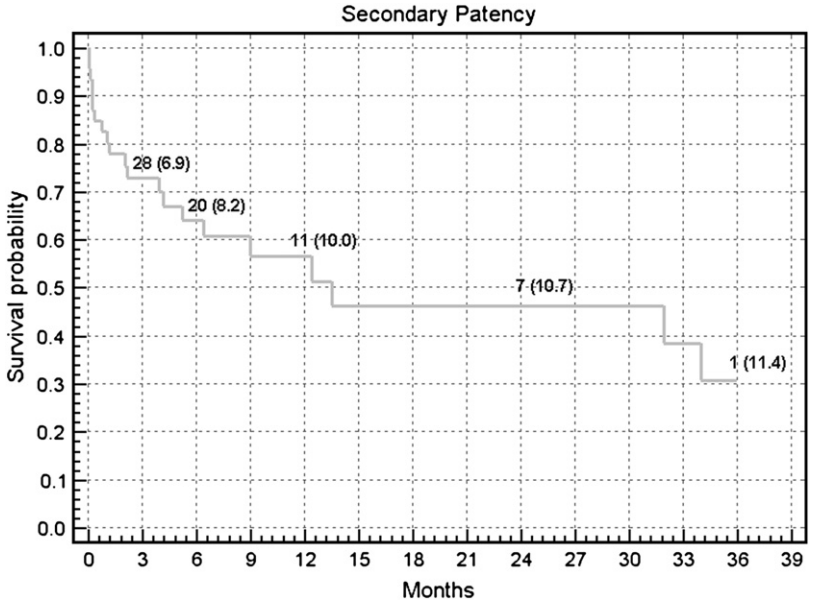

Fig. 3. Secondary patency curve for 46 revascularizations procedures with cold-stored venous allografts. Kaplan–Maier method. Number at rist (% SEM).

respectively. The secondary patency rate for the FK 506 immunosuppressed group was $76 \pm 9.3\%$ at 1 month, $65 \pm 10.8\%$ at 3 months, $65 \pm 10.8\%$ at 6 months and $44 \pm 19.1\%$ at 12 months, and for the other group $88 \pm 6.5\%$ at 1 month, $79 \pm 8.3\%$ at 3 months, $65 \pm 9.9\%$ at 6 months and $60 \pm 10.5\%$ at 12 months, respectively.

No statistical differences in patient survival, limb salvage rate, primary and secondary patency rates were observed between the groups using Wilcoxon's signed rank test.

Discussion

In this study, the greater saphenous veins obtained from brain-dead donors in the course of a multi-organ harvest were used in 43 patients with critical lower limb ischaemia. All vascular reconstructions were

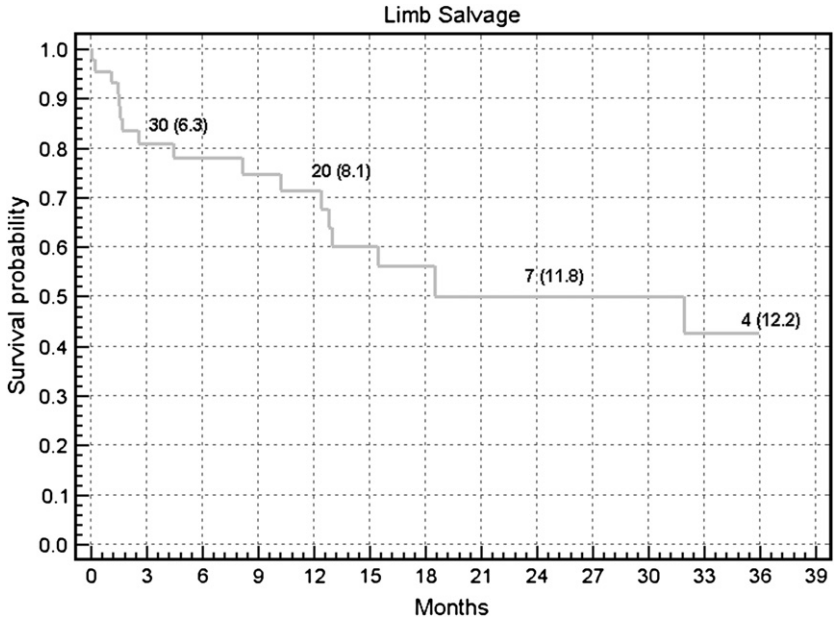

Fig. 4. Limb salvage curve for 44 critically ischaemic limbs treated by cold-stored venous allografts reconstructions. Kaplan–Maier method. Number at rist (% SEM).

performed as limb-salvage procedures. The ipsilateral autogenous greater saphenous vein was not available in any of presented patients, and almost 70% of them had diabetes mellitus.

Venous allografts are used in patients with no suitable autogenous vein when polytetrafluoroethylene (PTFE) grafts are not recommended. This concerns mainly patients with gangrene or poor run-off.[1] There are various types of venous allografts that can be used, which differ in how they are preserved. The most frequently used ones are glutaraldehyde venous allografts, followed by cryopreserved and cold-stored venous allografts.[18,19] However, a direct comparison between various allografts or preservation techniques is not possible because of the heterogeneity of individual studies and the absence of a study directly comparing various types of allografts.[18] A Meta-Analysis[19] suggests that there are probably no statistically significant differences between the various types of allografts.

Currently, only four studies describing the use of venous allografts preserved at 4° for infrainguinal bypasses have been published: Van Reedt Dortland *et al.*,[20] de Leersnijder *et al.*,[21] Rebane *et al.*[22] and Streinchenberger *et al.*[10] (Table 6) Nevertheless, all of these studies were undertaken on venous allografts that were harvested during varicose vein surgery. The grafts were stored in a saline solution containing antibiotics. Because of the difficult assembly of venous allografts, most of them were used as a part of composite grafts made with either polytetrafluoroethylene or polyurethane prostheses,[10] or were composed of more than two vein segments to obtain a conduit of a convenient length.[21,22] The cold ischaemic time ranged from 10 days[22] to six months[21] and no immunosuppressive drugs were used in postoperative protocols (Table 6). Diabetes was the only factor independently associated with a worse outcome in one study of cryopreserved venous allografts.[23]

Our cohort of patients differs from that in the previously mentioned studies of venous allograft reconstructions. Most of our patients suffered from diabetes (70%) and ischaemic heart disease (61%), all of them have had critical ischaemia of the legs, 67% of allovenous bypasses were performed as the secondary procedure and the site of distal anastomosis were crural or pedal arteries in 61% of the total reconstructions. Nevertheless, the 1-year limb salvage (71%) and secondary patency rates (57%) presented in this study are comparable to that of cryopreserved (78%, 48%) or cold-stored venous allografts (76%, 64%) presented in the Meta-Analysis by Albers *et al.*[19]

Recent immunological studies have shown that venous allografts, cold-stored as well as cryopreserved,

Table 6. Main features of cold-stored venous allografts series published since 1990 compared with the most largest cohort of cryopreserved venous allografts published by Farber *et al.*[23]

Author	Year	*N*	Critical ischaemia (%)	DM (%)	IHD (%)	Graft harvest	CIT	Sec Rec (%)	Cruropeda anast. (%)	Composite graft (%)	1-Year SP	2-Year SP	3-Year SP	1-Year LS	2-Year LS	3-Year LS	Aneurysmal dilatation (%)
van Reed Dortland *et al.*[20]	1991	104	100	16	48	Strip	6 w	38	42	100	74	66	55	87	85	85	15
De Leersnijder *et al.*[21]	1992	100	41	21	20	Strip	6 m	29	18	100	79	63	46	?	?	74	15
Rebane *et al.*[22]	1997	107	100	8	26	Strip	10 d	38	63	100	65	53	38	68	59	46	0.04
Streichenberger *et al.*[10]	2000	170	71	26	39	Strip	?	45	27	79	74	60	54	?	?	84	20
Present study	2006	46	100	70	61	MO	5 d	67	61	13	57	46	31	71	50	43	0
Farber *et al.*[23]	2003	199	89	58	?	Cryo	Cryo	50	62	?	30	24	?	80	71	?	44

DM, diabetes mellitus; *IHD*, ischaemic heart disease; *CIT*, cold ischaemic time; *Sec Rec*, secondary reconstruction; *SP*, secondary graft patency; *LS*, limb salvage; *Strip*, venous grafts obtained during varicose vein surgery; *MO*, venous grafts obtained during multiorgan harvest; *Cryo*, cryopreserved venous grafts.

are antigenic[24] and that the antigenicity is not modified by cryopreservation.[25–27] Immunosuppression has been examined as a possible adjunct to decrease the antigenicity of the venous allograft, mainly in animal models.[28–30] The immunosuppressive therapy after allovenous reconstructions is generally not used. Posner *et al*.[31] evaluated a combination of low-dose cyclosporine, azathioprime, prednisone, warfarin, aspirin and vasodilators on the patency of cryopreserved vein bypasses in humans and found a significantly improved patency (59% vs. 17%) at 1 year. Carpenter and Tomaszewski,[32] however, were unable to show any benefit to low-dose immunosuppression with azathioprime when compared to controls in regard to graft patency or limb salvage.

The drug used most frequently as an immunosuppressant in the beginning of our study was prednisone. From September 2004 we started to use an immunosuppressive protocol composed of oral FK 506 (tacrolimus, Prograf®, Astellas Pharma Ltd.) with drug blood level between 4 to 7 ng/ml. FK 506 is a modern immunosuppressant used widely after solid organ transplantations. Tacrolimus- when compared to cyclosporine-based immunosuppressive therapy in kidney transplantations, resulted in a significantly reduced risk of graft failure, without an increase in the incidence of adverse events.[33,34] Moreover, the inhibition of the transforming growth factor − beta (TGF-beta) production by FK 506 could make the drug eligible for use in vascular surgery.[35,36] TGF-beta is an important cytokine involved in the process of fibrosis. Increased expression of TGF-beta mRNA is associated with saphenous vein bypass graft disease and with postangioplasty stenosis.[37]

FK 506 was administered as a monotherapy in low dosages to our patients and no adverse effects have so far been observed. In comparison to other studies, no aneurysmal dilatation occurred in any of the patients (Table 6). This may have resulted from immunosuppression of the immune system, the short duration of the cold-stored preservation period, as well as the properties of preservation solution used. However, these observations need to be studied more consistently to be confirmed. The study reflects all the disadvantages associated with non-randomised, retrospective, single-center studies. The small sample size and the short follow-up period are other limitations.

In conclusion, femoral-infrapopliteal bypass using cold-stored saphenous vein allograft is an acceptable alternative for limb salvage when an autogenous vein is unavailable and the use of a prosthetic graft is not recommended. Only a vascular surgery unit closely integrated with a Transplant Center has the opportunity to use this type of allogenous material.

Acknowledgement

The work was supported by Grant No. MZO 00023001 awarded by Ministry of Health of the Czech Republic.

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Accepted 1 April 2007
Available online 15 June 2007