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René W. S. Chang
Susan Snowden
Andrew Palmer
Jonathan T. C. Kwan
Michael Nicholson
S. Habib Kashi
Ossie N. Fernando
Ferenc Perner
Guy H. Neild

European randomised trial of dual versus triple tacrolimus-based regimens for control of acute rejection in renal allograft recipients

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R.W.S. Chang (✉) · S. Snowden
Department of Renal Transplantation,
St. George's Hospital, Black Shaw Road,
London SW17 0QT, UK
e-mail: renechang@compuserve.com
Fax: + 44-208-725 2068

A. Palmer
St. Mary's Hospital, Renal Transplant Unit,
Praed Street, London W2 1NY, UK

J.T.C. Kwan
Department of Nephrology,
South West Thames Renal Unit,
St. Helier Hospital, Wrythe Lane,
Carshalton, Surrey SM5 1AA, UK

M. Nicholson
University Department of Surgery,
Leicester General Hospital NHS Trust,
Gwendolyn Road, Leicester LE5 4PW, UK

S.H. Kashi
Transplant Unit, Walsgrave General
Hospital, Clifford Bridge Road,
Walsgrave CV2 2DX, UK

O.N. Fernando
Department of Nephrology and
Transplantation, Royal Free Hospital,
Pond Street, London NW3 2QG, UK

F. Perner
Semmelweis Medical University,
Transplantation and Surgical Clinic,
Baross Utca 23, 1082 Budapest, Hungary

G.H. Neild
University College London Medical
School, Division of Nephrology,
The Middlesex Hospital, Mortimer Street,
London W1N 8AA, UK

Abstract Two large multicentre studies have shown superiority of tacrolimus-based immunosuppressive regimens compared with standard cyclosporine-based therapy in renal transplantation. In these studies, tacrolimus was used in a triple drug regimen of tacrolimus, corticosteroids, and azathioprine. The present study aimed to determine whether a tacrolimus-based dual regimen achieves a similar efficacy and safety profile compared with conventional triple therapy. In this prospective, open, multicentre trial, 249 patients were randomised to receive either dual therapy (n = 125) of oral tacrolimus (initial daily dose of 0.2 mg/kg) and oral prednisone or additionally, as a triple therapy (n = 124), oral azathioprine. The primary endpoint was the incidence of acute rejection at month 3. In addition, all patients were included into a follow-up evaluation at 1 year after transplantation. Both treatment groups had similar baseline characteristics. At month 3, patient survival was 97.6% (dual) and 96.7% (triple); graft survival was 92.7% (dual) and 91.7% (triple). The incidence of treated acute rejection confirmed by biopsy was 27.4% (dual) and 24.8% (triple); difference 2.6%, 95% CI [–9.4%–12.9%], P = 0.755. The incidence of corticosteroid-resistant rejection (biopsy-confirmed) was 9.7% (dual) and 10.7% (triple). The overall adverse events profile was similar; leukopenia (1.6% vs 11.6%, P = 0.002) was more frequent with triple therapy. Between months 4 and 12, six (dual) and eight (triple) patients had a rejection. At month 12, patient survival was 95.6% (dual) and 93.6% (triple); graft survival was 91.8% (dual) and 90.7% (triple). Tacrolimus proved to be efficacious and safe with both dual and triple low-dose regimens. The addition of azathioprine to a tacrolimus/corticosteroid-based therapy did not result in an increased efficacy.

Keywords Immunosuppression · Kidney transplantation · Acute rejection · Tacrolimus

Abbreviations *ITT* Intention to treat

Introduction

Tacrolimus (FK506) was first used clinically as a new immunosuppressive agent to rescue renal allografts in patients experiencing rejections unresponsive to cyclosporine [5] and in patients suffering from cyclosporine toxicity [1, 6]. Large multicentre trials comparing cyclosporine and tacrolimus in triple regimens were conducted in the United States [9] and Europe [8]. The studies showed significantly lower incidences of acute and biopsy-proven acute rejection in the tacrolimus groups 12 months after transplantation [8, 9]. In these studies, tacrolimus was used in a triple drug regimen of tacrolimus, corticosteroids, and azathioprine, and most units continue to use a triple drug regimen after renal transplantation.

Here we report a comparison of a tacrolimus-based dual therapy with triple therapy in a predominantly British renal transplant population. This study provides clinicians with data for the decision between dual and triple tacrolimus-based immunosuppressive regimens in renal transplantation.

Patients and methods

Trial design

Seven centres in the United Kingdom and one centre in Hungary participated in this prospective, randomised, open, parallel group phase-III/IV study. Patients were randomly assigned in a 1:1 ratio to receive either a tacrolimus-based dual (tacrolimus/corticosteroids) or triple (tacrolimus/corticosteroids/azathioprine) immunosuppressive regimen. Approval of the local ethics committees was obtained before the commencement of the study. The study was conducted according to the guidelines for good clinical practice as defined by the Declaration of Helsinki [2] and the European Community [3].

Randomisation was performed prior to transplantation. The treatment allocation schedule was generated centrally in blocks and stratified by centre and patient age (less than or more than 60 years). Individual patients were randomised by telephone using an interactive voice response system that provided a 24-h randomisation facility. After written informed consent was obtained, male or female patients aged 18 years or older were randomised. Patients were excluded if they were intolerant to steroids, macrolide antibiotics or tacrolimus, or if they required induction therapy with immunosuppressive antibody preparations. Patients known to be HIV-, HBV-, or HCV-positive were also excluded. Moreover, patients who had received or were receiving another organ transplant, other than a kidney, were excluded.

Treatment protocol

An initial oral tacrolimus dose of 0.1 mg/kg b.i.d. was recommended, and adjustments were to be made in steps of 25% to maintain whole blood trough levels in the range of 8–15 ng/ml. Patients in the dual therapy group received 500 mg or less methylprednisolone intravenously on day 0 (day of reperfusion) and 125 mg on day 1, followed by oral once-daily doses of 20 mg prednisone tapered to a daily dose of 5 mg on day 43, to be maintained until day 90. Triple immunosuppressive therapy was as above, with the addition of azathioprine as an intravenous bolus of 2 mg/kg on day 0, followed by an oral regimen of 1–2 mg/kg for the remainder of the study. The whole blood trough level of tacrolimus was monitored using a microparticle enzyme immunoassay (Abbott IMx Tacrolimus II MEIA).

Rejection assessment and classification

In the case of clinical signs of rejection, a renal biopsy was performed and assessed by the local histopathologist. An acute rejection was considered corticosteroid-sensitive if it resolved with corticosteroid treatment alone (500 mg i.v. bolus for 3 consecutive days). Rejections that did not respond to steroid bolus therapy were categorised as corticosteroid-resistant acute rejections. Corticosteroid-resistant acute rejections were subclassified as *antibody-sensitive* if they resolved after antilymphocyte antibody (OKT3 or ALG/ATG) treatment, or as *refractory acute rejection* if they remained unresolved after treatment with antibodies or were ongoing at study end or withdrawal.

Study assessments, sample size, and statistical analysis

Efficacy endpoints were the 3-month incidence of treated acute rejection (primary endpoint), time to first acute rejection and incidence of first corticosteroid-resistant rejection, graft and patient survival, and renal function as measured by serum creatinine concentrations. Graft loss was defined as the patient's return to long-term dialysis or the physical removal of the kidney and included death with a functioning graft.

The sample size was based on a presumed incidence of first acute rejection within 3 months after transplantation of 25% of patients receiving a triple therapy regimen. It was estimated that a total of 250 evaluable patients (125 in either group) would be required to detect a 17% difference in rejection with a power of at least 80%. Statistical testing was performed at the 5% level (two-tailed).

The intention-to-treat (ITT) population was used for both efficacy and safety analysis. All randomised patients were considered if they were transplanted and received at least one dose of tacrolimus. Results of misrandomised patients were attributed to the randomised treatment. The incidence rates (rejection episodes, adverse events) were compared with the treatment groups using the χ^2-test or Fisher's exact test. Survival analyses were conducted using Kaplan-Meier methods, and comparisons were made between treatment groups using the Wilcoxon test [7]. Patients were censored at their last visit date or at the date of their withdrawal. Confidence intervals were calculated with the Greenwood's method as well as the more conservative Peto's method [4].

Results

Patient demographics and baseline characteristics

Of the 249 patients, 125 were randomised to the dual therapy group and 124 to the triple therapy group. Two patients in the triple therapy group were randomised and transplanted twice, but only on the first occasion

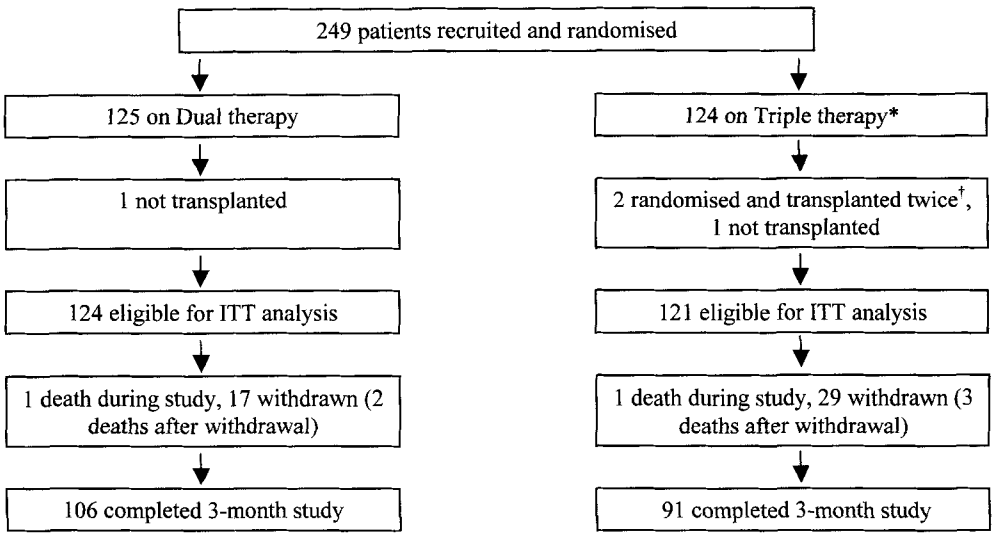

Fig. 1 Trial profile. *One patient was randomised to the triple therapy group but never received azathioprine, one patient who should have been randomised to the dual therapy group was included in the triple therapy group. †These patients were included in the intention-to-treat (*ITT*) cohort only on the first occasion

considered for the ITT cohort. One patient in each group was not transplanted and therefore excluded from analysis, leaving in the dual and triple therapy groups 124 and 121 patients, respectively, eligible for ITT analysis (Fig. 1). The majority of patients (231, 94.3%) were treated at centres in the United Kingdom, 14 (5.7%) patients were treated in Hungary.

A higher proportion of patients on dual therapy completed the study (85.5%) as compared with patients on triple therapy (75.2%). Seven deaths were reported; one patient in each treatment group died during the study, five deaths occurred after withdrawal. The predominant reason for withdrawal was protocol violation due to azathioprine administration: three patients in the dual therapy group received azathioprine for more than 7 days, and 17 patients in the triple therapy group discontinued azathioprine administration for more than 7 days. The second most common reason for withdrawal was graft loss (six patients in each treatment group). Two patients in the triple therapy group and no patient in the dual therapy group withdrew because of adverse events. Figure 1 shows the trial profile.

The treatment groups had similar demographic characteristics (Table 1). Also, donors' characteristics were evenly distributed between treatment groups. Tacrolimus dosing and whole blood trough levels decreased similarly in both groups during the study (Table 2).

Rejection

The number of patients who received treatment for clinically apparent rejections was similar in the two treatment groups (difference 0.6%, 95% CI [–11.7%–13.0%], $P = 0.922$, Table 3). The same was true for the incidence of corticosteroid-resistant acute rejection (difference –1.1%, 95% CI [–8.9%–6.8%], $P = 0.786$). The protocol stipulated that all clinically apparent rejection episodes had to be biopsied if medically feasible. The number of patients treated for biopsy-confirmed acute rejections was similar in both groups (dual therapy 27.4%, triple therapy 24.8%, difference 2.6%, 95% CI [–8.4%–13.6%], $P = 0.640$). The incidence of (biopsy-proven) corticosteroid-resistant rejection was also similar (9.7% vs 10.7%, difference –1.1%, 95% CI [–8.7%, + 6.5%], $P = 0.783$). The discrepancy in the number of patients with clinically apparent rejections and the number of patients with biopsy-proven rejections is largely due to negative biopsy results, i.e., the biopsies did not reveal signs of rejection or, in a few cases, provided insufficient samples for diagnosis. In total, 151 biopsies were performed in 80 patients in the dual therapy group and 131 biopsies were performed in 70 patients in the triple therapy group. In either treatment group, only three patients with clinically apparent rejection were not biopsied, i.e., in 97.5% of all acute rejection episodes a biopsy was performed.

Graft and patient survival

Graft survival after 3 months was marginally higher in patients on dual therapy (92.7%) than in patients on triple therapy (91.7%), $P = 0.784$, Wilcoxon test. The reasons for graft loss were comparable between groups (Table 4). In the dual therapy group, one patient died due to heart arrest, and a further two patients died after withdrawal due to CMV-pneumonitis and myocardial infarction, respectively. One patient in the triple therapy

Table 1 Baseline patient characteristics and donor characteristics

Characteristics	Dual therapy group ($n = 124$)	Triple therapy group ($n = 121$)	P value
Median age, years (range)			
Patients	48.0 (19–69)	45.0 (19–78)	0.340*
Donors	45.0 (18–73)	44.0 (8–70)	0.420*
Male sex, n of patients (%)	77 (62.1%)	82 (67.8%)	0.352†
Ethnic origin, n of patients (%)			
Caucasian	96 (77.4%)	92 (76.0%)	0.794‡
Black	10 (8.1%)	11 (9.1%)	
Oriental	1 (0.8%)	3 (2.5%)	
Other	17 (13.7%)	15 (12.4%)	
Cause of end-stage renal disease, n of patients (%)			
Chronic glomerulonephritis	22 (17.7%)	12 (9.9%)	
Interstitial pyelonephritis	4 (3.2%)	14 (11.6%)	
Diabetes type I and II	16 (12.9%)	13 (10.8%)	
Nephrosclerosis	2 (1.6%)	3 (2.5%)	
Polycystic disease	22 (17.7%)	21 (17.4%)	
Other/Unknown	58 (46.8%)	58 (47.9%)	
Mean HLA-antigen mismatches			
A/B/DR	1.08/1.07/0.73	0.97/1.15/0.65	
Mean cold ischaemia time, h (range)	20.4 (2–54)	21.3 (8–45)	0.356**
PRA grade, n of patients (%)			
0–< 50%	113 (95.8%)	104 (95.4%)	1.000‡
50–100%	5 (4.2%)	5 (4.6%)	
Not recorded	6	12	

* Wilcoxon rank sum test, † χ^2-test, ‡Fisher's exact test, ** Wilcoxon test

Table 2 Tacrolimus doses and blood trough levels. One patient (0.8%) in each treatment group received tacrolimus intravenously for 3 days

Time point	Dual therapy group ($n = 124$)			Triple therapy group ($n = 121$)		
	n	Mean	(SD)	n	Mean	(SD)
Tacrolimus daily dose (mg/kg)						
Week 1	124	0.17	(0.05)	121	0.17	(0.05)
Week 2	118	0.19	(0.09)	115	0.19	(0.08)
Week 3	119	0.20	(0.11)	112	0.20	(0.10)
Week 4	117	0.20	(0.11)	111	0.20	(0.12)
Month 2	116	0.19	(0.11)	109	0.18	(0.10)
Month 3	107	0.16	(0.10)	96	0.17	(0.10)
Tacrolimus whole blood trough levels (ng/ml)						
Week 1	122	15.39	(6.59)	120	16.49	(9.19)
Week 2	119	11.63	(4.61)	115	12.56	(6.68)
Week 3	115	11.50	(3.82)	105	12.78	(5.37)
Week 4	115	12.12	(4.01)	110	12.70	(5.69)
Month 2	115	12.09	(3.01)	108	11.96	(3.68)
Month 3	106	11.16	(2.86)	94	11.70	(5.17)

group died due to heart arrest and haemorrhage, and three patients died after withdrawal due to peritonitis, septicaemia and sudden death, respectively. By the end of month 3, the patient survival rates were 97.6% and 96.7% for the dual and triple therapy group, respectively ($P = 0.685$, Wilcoxon test, Table 4).

Adverse events and infections

The overall pattern of adverse events was similar in both treatment groups. The adverse event most frequently reported was hypertension (dual: 40/124, 32.2%, triple: 32/121, 26.4%). However, a high proportion of patients (dual: 40/107, 40.2%; triple: 30/96, 31.2%) was off antihypertensive drugs by month 3. Ad-

Table 3 Frequency of rejection based on patients

	Dual therapy group ($n = 124$)	Triple therapy group ($n = 121$)	P value
Patients with treated acute rejection	52 (41.9%)	50 (41.3%)	0.922*
Corticosteroid-resistant	13 (10.5%)	14 (11.6%)	0.786*
Antibody-sensitive	8 (6.5%)	10 (8.3%)	0.587†
Refractory**	6 (4.8%)	4 (3.3%)	0.749†
Patients with treated acute rejection confirmed by biopsy	34 (27.4%)	30 (24.8%)	0.755*
Corticosteroid-resistant	12 (9.7%)	13 (10.7%)	0.783*
Antibody-sensitive	8 (6.5%)	10 (8.3%)	0.587*
Refractory**	5 (4.0%)	3 (2.5%)	0.722†
Histological grade of acute rejection‡			
Banff grade I	13 (10.5%)	15 (12.4%)	0.472‡‡
Banff grade II	13 (10.5%)	10 (8.3%)	
Banff grade III	9 (7.3%)	7 (5.8%)	

*χ^2-test, †Fisher's exact test, **rejections ongoing at study end or time of withdrawal, ‡biopsies by patient; one patient could have had more than one biopsy with more than one grade, ‡‡Wilcoxon test

Table 4 Graft survival and patient survival

	Dual therapy ($n = 124$)	Triple therapy ($n = 121$)	P value* [95% CI]
Graft survival rate at month 3 (Kaplan-Meier method)	92.7%	91.7%	0.784* [−5.7% − + 7.7%]†
Cause of graft loss during study			
Died (during study)	1 (0.8%)	1 (0.8%)	
Rejection	2 (1.6%)	0 (0.0%)	
Initial nonfunction	2 (1.6%)	2 (1.7%)	
Technical reasons	1 (0.8%)	3 (2.5%)	
Infection	1 (0.8%)	0 (0.0%)	
Thrombosis	1 (0.8%)	2 (1.7%)	
Haemorrhage	0 (0.0%)	1 (0.8%)	
Hypotension	1 (0.8%)	0 (0.0%)	
Cause of graft loss after withdrawal			
Death (after withdrawal)	2 (1.6%)	3 (2.5%)	
Rejection	0 (0.0%)	1 (0.8%)	
Patient survival rate at month 3 (Kaplan-Meier method)	97.6%	96.7%	0.685* [−3.3% − + 5.1%]‡ [−3.3% − + 5.0%]**

*Wilcoxon test for treatment difference over 3 months, †Greenwood's and Peto's 95% CI for treatment difference at month 3, ‡Greenwood's 95% CI for treatment difference at month 3, **Peto's 95% CI for treatment difference at month 3

verse events reported with an incidence of at least 20% in either treatment group were creatinine increased, hyperkalemia, kidney tubular necrosis, infection, constipation, urinary tract infection, and anemia. A significant difference was found for leukopenia (dual 2/124 [1.6%], triple 14/121 [11.6%], $P = 0.002$, Fisher's exact test), and constipation (dual: 27/124 [21.8%]; triple: 12/121 [9.9%], $P = 0.014$, Fisher's exact test). The overall incidence of infections, based on clinical or laboratory findings, treated or untreated, was the same in the dual therapy group (70/124, 56.5%) and the triple therapy group (69/121, 57.0%). This was true for each type of infection: bacterial (dual 29.0% vs triple 33.1%), viral (14.5% vs14.0%), fungal (10.5% vs 5.0%), protozoal (0.8% vs 0.0%), and unspecified infections (28.2% vs 25.6%). CMV infections were noted with similar frequency (eight patients on dual therapy and nine patients on triple therapy).

Moreover, only minor differences were found in the frequency of nephrological disorders, glucose metabolism disorders, cardiac events, and in changes of vital signs. The incidences of tremor were 16/124, 12.9% (dual therapy) and 11/121, 9.1% (triple therapy). The incidence of post-transplant diabetes mellitus, defined as long-term insulin treatment (> 30 consecutive days) in previously nondiabetic patients, was four patients (3.8%) of 105 patients on dual therapy and five patients (4.8%) of 104 patients on triple therapy. Mean total

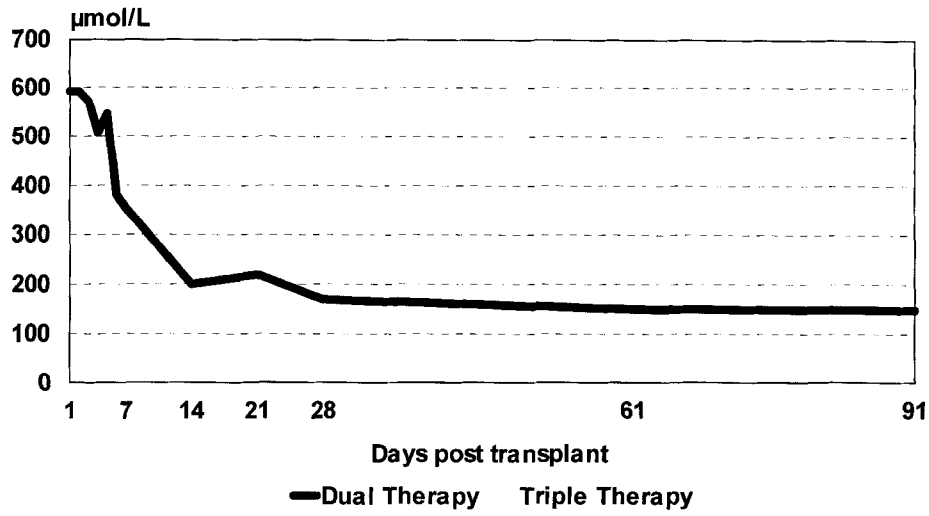

Fig. 2 Median serum creatinine. At day 91 the median serum creatinine levels were 149.0 µmol/l (dual) and 149.5 µmol/l (triple), Wilcoxon rank sum test, $P = 0.923$

cholesterol (± standard deviation) at screening was 5.43 (± 1.45) mmol/l in the dual therapy group and 5.32 (± 1.79) mmol/l in the triple therapy group. During month 3 the respective values were 5.23 (± 1.22) mmol/l for the dual therapy group and 5.18 (± 1.10) mmol/l in the triple therapy group. No patient in either therapy group was treated with lipid-lowering medication during the study.

Renal function improved similarly in both groups in the course of the study, at the end of month 3 the median serum creatinine levels were 149.0 µmol/l in the dual therapy group and 149.5 µmol/l in the triple therapy group (Fig. 2). Slight differences in laboratory data were apparent for haemoglobin, red blood cell count, and haematocrit: patients on triple therapy tended to shift more often to a value below the normal range at month 3 compared with patients on dual therapy.

Follow-up evaluation at 1 year after transplantation

In the dual group 104 patients (83.9 %) and in the triple group 101 patients (83.5 %) provided data at 1 year after transplantation. In the period of months 4 to 12, two (dual) and three (triple) patients died, patient survival at month 12 was 95.6 % (dual) and 93.6 % (triple). In the follow-up period, one graft was lost in either treatment group, due to refractory vascular rejection (dual) and noncompliance with subsequent refractory rejection (triple); graft survival was 91.8 % (dual) and 90.7 % (triple). At month 12, 78.7 % of patients were still on dual therapy; 2.1 % received triple therapy, 2.1 % were on tacrolimus monotherapy, 17.1 % received other regimens. Of the patients who were initially randomised to triple therapy, 65.6 % were still receiving triple therapy, 21.1 % of the patients were switched to dual therapy, 13.3 % of patients received other therapies. The median tacrolimus doses were 0.10 mg/kg (dual) and 0.095 mg/kg (triple), the median blood levels were 9.3 ng/ml and 8.8 ng/ml, respectively. Between months 4 and 12, new rejections occurred in six (dual) and eight (triple) patients; the rejections were resistant to steroids bolus treatment in one (dual) and three (triple) patients. At month 12, chronic rejection was reported for three (dual) and four (triple) patients. The incidence of tremor was 4.3 % (dual) and 4.5 % (triple), leukopenia was reported for one patient in the triple group. Other reported adverse events were infections (10.8 % vs 10.1 %), cardiovascular disorders (5.4 % vs 7.9 %), renal disorders (2.2 % vs 6.7 %), and urogenital disorders (3.2 % vs 5.6 %). In the triple therapy group two patients developed malignancies. Renal function was good 12 months after transplantation; the median serum creatinine levels were 147 µmol/l in the dual therapy group and 138 µmol/l in the triple therapy group.

Discussion

This European study, conducted predominantly at British transplantation centres, had a similar design as a study performed in Pittsburgh [10, 11]. The goal of keeping the switch between treatment arms to a minimum, in order to provide valid data, was successfully achieved. High patient and graft survival was observed in both tacrolimus-based dual therapy and triple therapy. Moreover, biopsy-proven rejection rates were low on dual therapy and on triple therapy; this was also true for the incidence of corticosteroid-resistant rejections. The overall safety profile of both dual and triple regimens was similar. The low-dose regimen of tacrolimus used in the present study resulted in a low incidence

of new-onset diabetes. No patient in either treatment group had to take lipid-lowering drugs during the study. Moreover, a high proportion of patients was off antihypertensive drugs at month 3. The safety profiles of treatment groups differed only in the incidence of constipation and leukopenia. The difference observed in the incidence of constipation does not pose a serious safety obstacle since it is a common adverse event in renal transplant populations and its incidence decreased with study duration. The significant difference determined in the incidence of leukopenia can be attributed to azathioprine. Therefore, patients developing leukopenia under triple therapy should be switched to a dual therapy regimen of tacrolimus and corticosteroids only.

At 1 year after transplantation, the high efficacy was sustained. Few new rejections were reported and kidney function assessed by serum creatinine was good. In respect to adverse events, the dual therapy group had a slightly favourable safety profile at month 12. In conclusion, tacrolimus proved to be efficacious and safe with both dual and triple regimens. The addition of azathioprine to a tacrolimus/corticosteroid-based therapy did not convey an increased efficacy.

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