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Improved Survival in Liver Transplant Recipients Receiving Prolonged-Release Tacrolimus in the European Liver Transplant Registry

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This study was a retrospective analysis of the European Liver Transplant Registry (ELTR) performed to compare long-term outcomes with prolonged-release tacrolimus versus tacrolimus BD in liver transplantation (January 2008–December 2012). Clinical efficacy measures included univariate and multivariate analyses of risk factors influencing graft and patient survival at 3 years posttransplant. Efficacy measures were repeated using propensity score-matching for baseline demographics. Patients with <1 month of follow-up were excluded from the analyses. In total, 4367 patients (prolonged-release tacrolimus: n = 528; BD: n = 3839) from 21 European centers were included. Tacrolimus BD treatment was significantly associated with inferior graft (risk ratio: 1.81; p = 0.001) and patient survival (risk ratio: 1.72; p = 0.004) in multivariate analyses. Similar analyses performed on the propensity score-matched patients confirmed the significant survival advantages observed in the prolonged-release tacrolimus- versus tacrolimus BD-treated group. This large retrospective analysis from the ELTR identified significant improvements in long-term graft and patient survival in patients treated with prolonged-release tacrolimus versus tacrolimus BD in primary liver

transplant recipients over 3 years of treatment. However, as with any retrospective registry evaluation, there are a number of limitations that should be considered when interpreting these data.

Abbreviations: BD, twice daily; ELITA, European Liver and Intestine Transplant Association; ELTR, European Liver Transplant Registry; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICU, intensive care unit; mITT, modified intent-to-treat; MELD, Model for End-stage Liver Disease; MELD-Na, MELD score including serum sodium concentration; MMF, mycophenolate mofetil; PK, pharmacokinetic; QD, once daily; SD, standard deviation; UNOS, United Network for Organ Sharing

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Introduction

Over the last 20 years, there have been significant advances in the success of liver transplantation. Excellent 1-year graft and patient survival rates (1,2) have shifted the focus of the transplant community towards improving long-term outcomes. This can be partially attributed to the advent of effective immunosuppressive therapies (1,3), with tacrolimus constituting the mainstay of immunosuppressive protocols. Over the last 10 years, 5-year graft survival rates for liver transplants have increased to around 63% (3). However, this may vary depending on the primary disease indication and type of liver transplant. Known factors that negatively influence the outcomes in liver transplantation include high Model for End-Stage Liver Disease (MELD) scores, elevated bilirubin, liver transplant urgency, re-transplant, donor age and cold ischemia time (2,4–6), as well as the viral status of the recipient, in particular, HCV and HIV infections. Other factors, such as non-adherence to immunosuppressive therapy and high intra-patient variability of tacrolimus exposure, may also negatively impact long-term outcomes (7–13).

Prolonged-release tacrolimus was licensed in Europe in 2007 for use in adult kidney or liver transplant recipients to prevent rejection (14). The European Medicines Agency suggested that a prolonged-release therapeutic action with this once-daily dosing formulation of tacrolimus may offer distinct advantages over an immediate-release action (14). In clinical trials comparing once-daily (QD), prolonged-release tacrolimus with tacrolimus twice daily (BD), a significant reduction in intra- and inter-patient variability in tacrolimus exposure, and a lower C_{max} with less variability in concentrations over time, was observed with prolonged-release tacrolimus in liver (15,16) and kidney transplant recipients (17). Due to the once-daily dosing regimen, prolonged-release tacrolimus has also been shown to improve adherence to therapy when compared with tacrolimus BD in multiple studies including randomized controlled trials (18–23). This is of particular importance as non-adherence rates have been reported to be 20–62%, depending on the method of reporting, in liver transplantation (11,13), which may contribute to graft loss, early and late acute rejection, and death (11,24). The outcomes from clinical trials are of relatively short duration; therefore, there remains a need for more data to assess the effect of prolonged-release tacrolimus on long-term outcomes in liver transplantation.

The aim of this study was to assess the impact of prolonged-release tacrolimus versus tacrolimus BD on long-term graft and patient survival using data from the ELTR. To our knowledge, this is the first large retrospective registry study in Europe evaluating prolonged-release tacrolimus-based immunosuppression in liver transplantation.

Methods

This study was a retrospective analysis of primary liver transplant patients receiving prolonged-release tacrolimus (Advagraf^{TM}; Astellas Pharma Europe Ltd., UK) and tacrolimus BD in the European Liver Transplant Registry (ELTR) database. The ELTR represents liver transplant data from 145 centers across Europe (3,25). Data from participating centers are collected on a voluntary basis at regular intervals using a two-part, standardized questionnaire designed by the ELTR Coordinating Committee to capture information on donors and recipients. Part 1 focuses on technical aspects of liver transplantation and induction immunosuppression. Part 2 comprises questions on posttransplant mortality, graft failure and maintenance immunosuppression during patient follow-up. Audits of contributing centers are randomly performed each year to assess the quality of the data. The methods used to populate the registry and obtain the data have been described previously (3,13,25). To prevent center bias, only the 21 centers who used both prolonged-release tacrolimus and tacrolimus BD were eligible for inclusion in this analysis.

Inclusion criteria

Data were collected prospectively from patients (≥18 years old) who underwent their first liver transplant between January 2008 and December 2012 from contributing centers across Europe. All patients included in this study received prolonged-release tacrolimus or tacrolimus BD, with or without concomitant immunosuppressants (including induction agents) within the first month after liver transplantation.

Clinical efficacy measures

In order to avoid the potential impact of early postoperative complications not associated with the immunosuppression regimen, all efficacy measures were analyzed using the modified intent-to-treat (mITT) population, which excluded all patients who had less than 1 month of follow-up posttransplant. The clinical efficacy measures included univariate and multivariate analyses of the risk factors influencing graft and patient survival; Kaplan–Meier estimates of the incidence of graft and patient survival stratified by prolonged-release tacrolimus- and tacrolimus BD-based immunosuppression; and causes of graft loss and mortality. Treatment groups were stratified by prolonged-release tacrolimus or tacrolimus BD treatment during the first month posttransplant, and for the purpose of these analyses patients remained in these allocated groups regardless of any changes in immunosuppression during the 3-year follow-up.

Propensity score matching: In order to account for differences in donor and recipient baseline characteristics between groups when estimating the effect of treatment on outcomes, the clinical efficacy measures were repeated on a propensity score-matched population. Prolonged-release tacrolimus and tacrolimus BD groups were paired on a 1:2 ratio according to items with similar values. The propensity score was based on recipient age, recipient HIV, HCV and HCC status, UNOS status, creatinine levels, donor age, date of transplantation, total ischemia time and administration of other immunosuppressive medications early posttransplant (ciclosporin, mycophenolate mofetil [MMF], corticosteroids, daclizumab and basiliximab). All unmatched units in both the prolonged-release tacrolimus and tacrolimus BD groups were excluded from the propensity score-matched population. Due to the number of potential confounding variables considered, this resulted in a lower number of patients available for the analysis.

Statistical analyses

Statistical analyses were performed using SAS software Version 9.1.3 (SAS Institute Inc., Cary, NC). A univariate Cox regression analysis was performed to evaluate the risk factors influencing graft and patient survival after liver transplantation. Data from the univariate analyses were reported using log-rank p-values, with $p < 0.05$ considered to be statistically significant. A Cox proportional hazards regression evaluation ($p < 0.15$) was used in a multivariate model to assess the impact of donor and recipient variables on graft and patient survival. Patients with missing data on the ELTR questionnaire were excluded from the multivariate analyses. Kaplan–Meier analyses were used to estimate graft and patient survival stratified by treatment group; statistical analyses were performed using the log-rank test ($p < 0.05$).

Results

Donor and recipient characteristics and demographics

Patient population: In total, 4367 primary liver transplant recipients were included in this analysis (Figure 1). All recipients received either prolonged-release tacrolimus (n = 528) or tacrolimus BD (n = 3839). Since prolonged-release tacrolimus (Advagraf) was licensed for use in 2007 (14) and enrolment in the study was between 2008 and 2012, the proportion of patients who received prolonged-release tacrolimus during Month 1 increased gradually over the study period.

Baseline characteristics: Baseline characteristics of donors and recipients were generally comparable between groups with the main exception being older recipients and younger donors in the prolonged-release tacrolimus versus tacrolimus BD group ($p = 0.002$ and $p = 0.004$, respectively) (Table 1).

Concomitant medications: A significantly higher number of patients received MMF in the prolonged-release tacrolimus versus tacrolimus BD group (93.6 vs. 65.8%, respectively; $p < 0.0001$). Significantly fewer patients treated with prolonged-release tacrolimus received corticosteroid induction therapy (58.5 vs. 94.7%; $p < 0.0001$). However, a similar proportion of patients in each group received maintenance corticosteroid therapy (26.0 vs. 29.5%; $p = 0.11$). In total, 54.2% of prolonged-release tacrolimus and 61.4% of tacrolimus BD patients received both MMF and corticosteroids ($p = 0.001$).

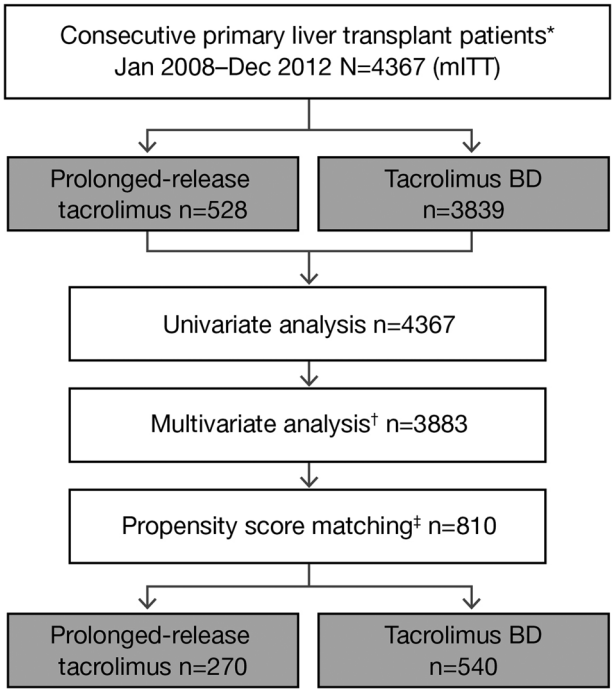

Figure 1: Diagrammatic representation of the patient populations. *Analysis only in centers using prolonged-release tacrolimus and tacrolimus BD; †Patients with missing data points for items on the ELTR questionnaire were excluded from the multivariate analysis; ‡Propensity score matching ratio 1:2 prolonged-release tacrolimus:tacrolimus BD; BD, twice daily, mITT, modified intent-to-treat. Correction made after online publication February 19, 2015: Figure 1 has been updated.

Analyses of patients with ≥1 month of follow-up

Univariate and multivariate analyses: In the univariate analysis, tacrolimus BD during the first month posttransplant was identified as a significant risk factor for inferior graft survival ($p = 0.01$) but not patient survival ($p = 0.07$). Other factors that significantly contributed to reduced long-term graft and patient survival are listed in Table 2.

In the multivariate analysis, tacrolimus BD was also found to be an independent risk factor for inferior graft survival (risk ratio: 1.81; 95% confidence interval: 1.26–2.61; $p = 0.001$) and inferior patient survival (risk ratio: 1.72; 95% confidence interval: 1.19–2.49; $p = 0.004$). Other factors that significantly contributed to reduced long-term graft and patient survival are listed in Table 3.

Kaplan–Meier analyses: Kaplan–Meier analysis demonstrated significantly improved graft survival over 3 years in patients treated with prolonged-release tacrolimus versus tacrolimus BD ($p = 0.01$) (Figure 2A). At Year 3, an 8% improvement in graft survival was observed in the prolonged-release tacrolimus versus tacrolimus BD group. A numerical but not statistically significant improvement in patient survival over 3 years was also observed in patients

Table 1: Baseline characteristics of donors and liver transplant recipients

		mITT population			Propensity score-matched patients[1]		
Parameter	Category	Prolonged-release tacrolimus (n=528)	Tacrolimus BD (n=3839)	p-value[2]	Prolonged-release tacrolimus (n=270)	Tacrolimus BD (n=540)	p-value[2]
Donor characteristics							
Age, years	Mean (SD)	49.6 (19.0) (n=512)	52.1 (18.1) (n=3697)	0.004	50.4 (18.9) (n=262)	51.6 (19.0) (n=519)	0.38
Gender, n (%)	Female	216 (41.5)	1685 (44.3)	0.23	105 (38.9)	228 (42.7)	0.3
	Male	305 (58.5)	2122 (55.7)		165 (61.1)	306 (57.3)	
Recipient characteristics							
Age, years at first transplant	Mean (SD)	53.6 (10.6) (n=528)	52.1 (11.4) (n=3839)	0.002	52.6 (11.0) (n=270)	52.5 (11.0) (n=540)	0.9
	≥60 years, n (%)	165 (31.3)	990 (25.8)	0.008	73 (27.0)	142 (26.3)	0.82
	≥65 years, n (%)	56 (10.6)	335 (8.7)	0.16	30 (11.1)	55 (10.2)	0.69
	≥70 years, n (%)	9 (1.7)	34 (0.9)	0.09	7 (2.6)	8 (1.5)	0.28
Gender, n (%)	Female	165 (31.4)	1265 (33.0)	0.45	84 (31.1)	181 (33.5)	0.49
	Male	361 (68.6)	2568 (67.0)		186 (68.9)	359 (66.5)	
Body mass index	Mean (SD)	26 (4.7) (n=507)	25.7 (4.7) (n=3627)	0.11	25.9 (4.5) (n=264)	25.6 (4.6) (n=511)	0.37
Recipient health status and indication for transplant							
HBsAg, n (%)	Negative	449 (90.2)	3104 (88.8)	0.35	241 (90.3)	476 (89.6)	0.78
	Positive	49 (9.8)	393 (11.2)		26 (9.7)	55 (10.4)	
HBV DNA, n (%)	Negative	160 (89.4)	1056 (84.8)	0.10	49 (84.5)	100 (85.5)	0.86
	Positive	19 (10.6)	190 (15.2)		9 (15.5)	17 (14.5)	
Co-existing HBV and delta virus, n (%)	Negative	127 (95.5)	351 (87.1)	0.007	24 (100)	38 (79.2)	0.03
	Positive	6 (4.5)	52 (12.9)		0 (0)	10 (20.8)	
Anti-HCV, n (%)	Negative	379 (75.3)	2611 (74.4)	0.64	222 (82.2)	445 (82.4)	0.95
	Positive	124 (24.7)	899 (25.6)		48 (17.8)	95 (17.6)	
HCV RNA, n (%)	Negative	115 (60.2)	819 (60.5)	0.93	38 (58.5)	78 (60.5)	0.79
	Positive	76 (39.8)	534 (39.5)		27 (41.5)	51 (39.5)	
HIV serology, n (%)	Negative	527 (99.8)	3798 (98.9)	0.06	269 (99.6)	540 (100)	0.33
	Positive	1 (0.2)	41 (1.1)		1 (0.4)	0 (0)	
Main indication for transplant, n (%)	Acute liver disease	26 (4.9)	235 (6.1)	0.6	14 (5.2)	21 (3.9)	0.04
	Cancer	122 (23.1)	932 (24.3)		48 (17.8)	132 (24.4)	
	Cirrhosis	293 (55.5)	2061 (53.8)		149 (55.2)	303 (56.1)	
	Other	87 (16.5)	601 (15.7)		59 (21.9)	84 (15.6)	
HCC (primary or secondary disease), n (%)	No	361 (68.4)	2807 (73.3)	0.02	203 (75.2)	405 (75)	0.95
	Yes	167 (31.6)	1022 (26.7)		67 (24.8)	135 (25)	
	HCC with cirrhosis	163 (30.9)	957 (25.0)	0.004	—	—	
Criteria for first liver transplant							
Liver transplant urgency,[3] n (%)	No	346 (86.1)	2410 (93.0)	<0.0001	155 (89.1)	359 (92.5)	0.18
	Yes	56 (13.9)	182 (7)		19 (10.9)	29 (7.5)	

Table 1: Continued

Parameter	Category	mITT population: Prolonged-release tacrolimus (n=528)	mITT population: Tacrolimus BD (n=3839)	mITT population: p-value[2]	Propensity score-matched patients[1]: Prolonged-release tacrolimus (n=270)	Propensity score-matched patients[1]: Tacrolimus BD (n=540)	Propensity score-matched patients[1]: p-value[2]
UNOS status,[4] n (%)	1	37 (7.3)	367 (9.6)	<0.0001	22 (8.1)	39 (7.2)	0.72
	2	60 (11.8)	432 (11.4)		28 (10.4)	60 (11.1)	
	3	267 (52.6)	2367 (62.2)		144 (53.3)	306 (56.7)	
	4	144 (28.3)	638 (16.8)		76 (28.1)	135 (25.0)	
MELD score	Mean (SD)	17.3 (8.9) (n=522)	18.1 (10.0) (n=3758)	0.08	17.6 (9.1) (n=267)	16.8 (8.6) (n=535)	0.26
MELD-Na score	Mean (SD)	27.8 (12.3) (n=136)	29.0 (16.6) (n=1092)	0.32	27.8 (13.1) (n=70)	29.2 (26.0) (n=156)	0.58
Liver function and baseline laboratory values							
Child–Pugh class, n (%)	A	32 (12.0)	171 (7.5)	0.016	25 (21.0)	50 (15.2)	0.28
	B	127 (47.7)	1236 (54.2)		57 (47.9)	180 (54.5)	
	C	107 (40.2)	873 (38.3)		37 (31.1)	100 (30.3)	
Serum creatinine concentration, mg/dL	Mean (SD)	1.1 (0.7) (n=514)	1.2 (0.9) (n=3768)	0.005	1.1 (0.9) (n=270)	1.1 (0.9) (n=540)	0.8
Total bilirubin, mg/dL	Mean (SD)	5.8 (8.1) (n=517)	6.3 (9.2) (n=3773)	0.19	6.4 (8.9) (n=267)	5.5 (8.2) (n=534)	0.19

[1]Propensity-score matching was based on recipient age, recipient HIV, HCV and HCC status, UNOS status, creatinine levels, donor age, date of transplantation, total ischemia time and administration of induction immunotherapy (ciclosporin, mycophenolate mofetil, corticosteroids, daclizumab and basiliximab).
[2]P-value between treatment cohort comparisons.
[3]Liver transplant urgency was determined by the treating physician and indicated on the questionnaire by ''yes'' or ''no'' tick box.
[4]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization, 3. Continuous medical care, 4. At home with normal function.
BD: twice daily; HBsAg: HBV surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MELD: Model for End-stage Liver Disease; MELD-Na: MELD score including serum sodium concentration; mITT: modified intent-to-treat; SD: standard deviation; UNOS: United Network for Organ Sharing.

Table 2: Univariate analyses of risk factors for reduced graft and patient survival 1 and 3 years posttransplant after exclusion of patients with <1 month of follow-up

			Graft survival, %			Patient survival, %		
Parameters at first transplant	Category	N	1 year	3 years	p-value[1]	1 year	3 years	p-value[1]
Immunotherapy during Month 1	Prolonged-release tacrolimus	528	91	88	0.01	92	88	0.07
	Tacrolimus BD	3839	89	80		91	82	
Donor characteristics								
Donor sex	Female	1901	90	81	0.88	91	83	0.9
	Male	2427	89	81		91	83	
Donor age ≥50 years	Yes	2405	88	78	<0.0001	90	80	<0.0001
	No	1804	92	85		92	86	
Donor age ≥60 years	Yes	1500	88	77	0.0003	90	79	0.0008
	No	2709	90	83		91	85	
Macro/micro-vesicular graft steatosis	No	944	90	83	0.5	91	85	0.34
	Yes	676	90	81		90	82	
Blood group compatibility	Compatible	200	85	80	0.03	86	81	0.01
	Iso group	4033	90	81		91	83	
	Non-compatible	15	78	64		78	64	
Living donor	Yes	6	50	50	0.02	50	50	0.01
	No	4330	90	81		91	83	
Recipient characteristics								
Recipient sex	Female	1430	90	83	0.06	91	84	0.13
	Male	2929	89	80		90	82	
Recipient age ≥50 years	Yes	2907	88	79	0.0001	90	81	<0.0001
	No	1460	92	85		93	87	
Recipient age ≥60 years	Yes	1155	88	79	0.13	89	80	0.02
	No	3212	90	82		91	84	
Recipient dialysis	No	3598	90	82	<0.0001	91	84	<0.0001
	Yes	235	79	70		80	73	
Recipient viral status								
HBsAg	Negative	3553	89	80	0.19	90	82	0.08
	Positive	442	93	84		94	87	
Co-existing HBV and delta virus	Negative	478	84	78	0.03	85	79	0.01
	Positive	58	96	90		100	94	
Anti-HCV	Negative	2990	91	84	<0.0001	92	85	<0.0001
	Positive	1023	86	72		87	75	
HIV serology	Negative	4325	90	81	<0.0001	91	83	<0.0001
	Positive	42	71	44		70	50	
HCV RNA	Negative	934	91	83	<0.0001	91	84	0.001
	Positive	610	84	70		86	74	
Criteria for liver transplant								
Liver transplant urgency[2]	No	2756	90	81	0.39	90	82	0.25
	Yes	238	86	79		86	81	
UNOS status[3]	1	404	85	79	0.0001	86	80	0.0002
	2	492	84	76		85	79	
	3	2634	91	82		92	84	
	4	782	91	82		91	82	
UNOS status[3] 1 or 2	Yes	896	84	77	<0.0001	86	80	<0.0001
	No	3416	91	82		92	84	
MELD score	<14	1975	91	80	0.003	92	82	0.001
	14–25	1453	91	83		92	86	
	>25	852	85	79		85	80	
Liver function and laboratory values								
Recipient Child–Pugh class	A	723	90	77	0.0002	91	77	0.0001
	B	863	93	86		94	87	
	C	566	84	77		85	79	
Serum creatinine concentration ≥2mg/dL	Yes	353	78	72	<0.0001	79	73	<0.0001
	No	3929	91	82		92	84	

Table 2: Continued

Parameters at first transplant	Category	N	Graft survival, %			Patient survival, %		
			1 year	3 years	p-value[1]	1 year	3 years	p-value[1]
Indication								
Main indication for transplant	Acute liver failure	261	89	85	0.15	90	88	0.08
	Chronic liver disease	2677	90	83		91	85	
	Metabolic disease	204	88	81		89	84	
	Tumor (benign)	97	91	88		92	92	
	Tumor (malignant)	1054	90	75		91	77	
	Other	67	85	79		85	82	
Acute liver failure as main disease	Yes	261	89	85	0.53	90	88	0.35
	No	4096	90	81		91	83	
Cirrhosis as main disease	Yes	2354	89	82	0.58	90	84	0.66
	No	2003	90	80		91	82	
Cancer as main disease	Yes	1054	90	75	0.01	91	77	0.01
	No	3303	89	83		91	85	
Milan criteria (in patients with HCC)	Yes	872	91	81	<0.0001	93	83	<0.0001
	No	340	88	62		88	63	
HCC with tumor size >50mm	Yes	76	80	44	<0.0001	80	44	<0.0001
	No	1188	91	77		92	79	
Surgical procedure								
Total ischemia time	≥12 h	321	86	75	0.08	88	78	0.1
	8–12 h	1971	89	81		91	84	
	1–8 h	1981	91	81		91	83	
Total ischemia time ≥12 h	Yes	321	86	75	0.03	88	78	0.03
	No	3952	90	81		91	83	
Type of graft	Full size	4127	90	81	0.17	91	83	0.12
	Domino	57	90	73		90	76	
	Living	6	50	50		50	50	
	Reduced	9	83	83		83	83	
	Split	137	87	81		92	86	
Liver transplant	Heterotopic	15	93	93	0.91	93	93	0.97
	Orthotopic	4308	90	81		91	83	

[1]Log-rank p-value.
[2]Liver transplant urgency was determined by the treating physician and indicated on the questionnaire by ''yes'' or ''no'' tick box.
[3]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization, 3. Continuous medical care, 4. At home with normal function.
BD: twice daily; HBsAg: HBV surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MELD: Model for End-stage Liver Disease; UNOS: United Network for Organ Sharing.

treated with prolonged-release tacrolimus (6% improvement at Year 3) compared with tacrolimus BD ($p = 0.07$) (Figure 2B).

Propensity score-matched analyses

The propensity score-matched analysis was performed on 810 patients (prolonged-release tacrolimus: $n = 270$; tacrolimus BD: $n = 540$). Donor and recipient baseline characteristics were comparable between the two treatment groups for the propensity score-matched patients (Table 1).

Univariate and multivariate analyses: In the univariate analysis, the use of tacrolimus BD was a significant risk factor for reduced graft and patient survival ($p = 0.002$ and $p = 0.003$, respectively). Other factors that significantly contributed to reduced long-term graft and patient survival are listed in Table 4.

In the multivariate analysis, the use of tacrolimus BD was also a significant risk factor for reduced graft survival (risk ratio: 3.33; 95% CI: 1.85–5.99; $p < 0.0001$) and reduced patient survival (risk ratio: 3.33; 95% CI: 1.81–6.12; $p = 0.0001$). Other factors that significantly contributed to reduced graft and patient survival in the multivariate analysis are listed in Table 5.

Kaplan–Meier analyses: Kaplan–Meier analyses over 3 years showed a significant improvement in both graft and patient survival in prolonged-release tacrolimus- compared with tacrolimus BD-treated patients ($p = 0.002$ and $p = 0.003$) (Figure 3). Similar to the overall analyses, there was an 8% improvement in graft survival and a 7% improvement in patient survival in prolonged-release tacrolimus- versus tacrolimus BD-treated patients observed at Year 3.

Table 3: Multivariate analyses of risk factors for reduced (A) graft and (B) patient survival after exclusion of patients with <1 month of follow-up

Risk factors at first transplant	Risk ratio	95% Confidence interval	p-value
(A) Graft survival (N=3828)			
Recipient HIV-positive	3.40	2.04–5.68	<0.0001
Serum creatinine concentration ≥2 mg/dL	1.84	1.42–2.39	<0.0001
Tacrolimus BD immunotherapy	1.81	1.26–2.61	0.001
UNOS status[1] 1 or 2	1.61	1.30–2.00	<0.0001
Recipient anti-HCV positive	1.51	1.24–1.83	<0.0001
Total ischemia time of ≥12 h during first liver transplant	1.42	1.06–1.89	0.02
Recipient age ≥50 years	1.41	1.15–1.73	0.001
HCC (primary or secondary disease)	1.37	1.11–1.67	0.003
Donor age ≥50 years	1.33	1.10–1.60	0.003
(B) Patient survival (N=3883)			
Recipient HIV-positive	3.41	2.02–5.78	<0.0001
Serum creatinine concentration ≥2 mg/dL	1.86	1.42–2.43	<0.0001
Tacrolimus BD immunotherapy	1.72	1.19–2.49	0.004
UNOS status 1 or 2	1.62	1.30–2.04	<0.0001
Recipient age ≥50 years	1.52	1.22–1.88	0.0002
Recipient anti-HCV positive	1.47	1.20–1.80	0.0002
HCC (primary or secondary disease)	1.38	1.11–1.70	0.003
Donor age ≥50 years	1.33	1.10–1.61	0.004

[1]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization.
BD: twice daily; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; UNOS: United Network for Organ Sharing.

Causes of graft loss and mortality

A lower incidence of graft loss was reported in the prolonged-release tacrolimus versus the tacrolimus BD group over 3 years of treatment. The most common cause of graft loss was infection (Table 6). At Year 3, bacterial infection that resulted in graft loss was more frequent in patients treated with prolonged-release tacrolimus versus tacrolimus BD ($p < 0.0001$) (Table 6). There were no significant differences between groups in the incidence of graft loss due to acute or chronic rejection, cardiovascular, cerebrovascular or renal causes.

Patient mortality was proportionally lower in the prolonged-release tacrolimus versus tacrolimus BD group. The most common cause of patient mortality was infection in both groups (Table 6), although bacterial infection resulting in patient mortality was more frequent in patients treated with prolonged-release tacrolimus versus tacrolimus BD ($p < 0.0001$). There were no significant differences between treatment groups in the proportion of patients with cardiovascular, cerebrovascular or renal causes of mortality.

Propensity score-matched patients: No significant differences in the causes of graft loss and mortality were observed between the groups with the exception of gastrointestinal complications, which were significantly higher in the prolonged-release tacrolimus versus tacrolimus BD arm ($p = 0.04$ for both comparisons).

Discussion

Data from the ELTR in adult primary liver transplantation confirm that tacrolimus-based immunosuppression is associated with good 3-year graft and patient survival. Univariate analyses confirmed the independent prognostic value of classical risk factors beyond MELD score ≥25, including donor and recipient age (≥50 years), recipient viral status (HIV- and HCV-positivity), and UNOS status 1 or 2 in impairing Month 1 to Year 3 graft and patient survival. The use of tacrolimus BD was also a significant and independent risk factor for reduced graft and patient survival over 3 years of treatment, which was confirmed in multivariate analyses. However, it is important to recognize that there were differences in donor and recipient baseline characteristics between the groups, which may have affected the long-term outcomes. In an effort to account for these differences, propensity score-matched analyses were performed. The improved graft and patient survival observed in the prolonged-release tacrolimus group versus the tacrolimus BD group was confirmed in both the univariate and multivariate analyses performed on these propensity score-matched patients.

In the Kaplan–Meier analyses, improvements in graft and patient survival in prolonged-release tacrolimus- versus tacrolimus BD-treated patients began to emerge as early as 3 months and continued to increase over the 3-year period posttransplant. By Year 3, there was a statistically

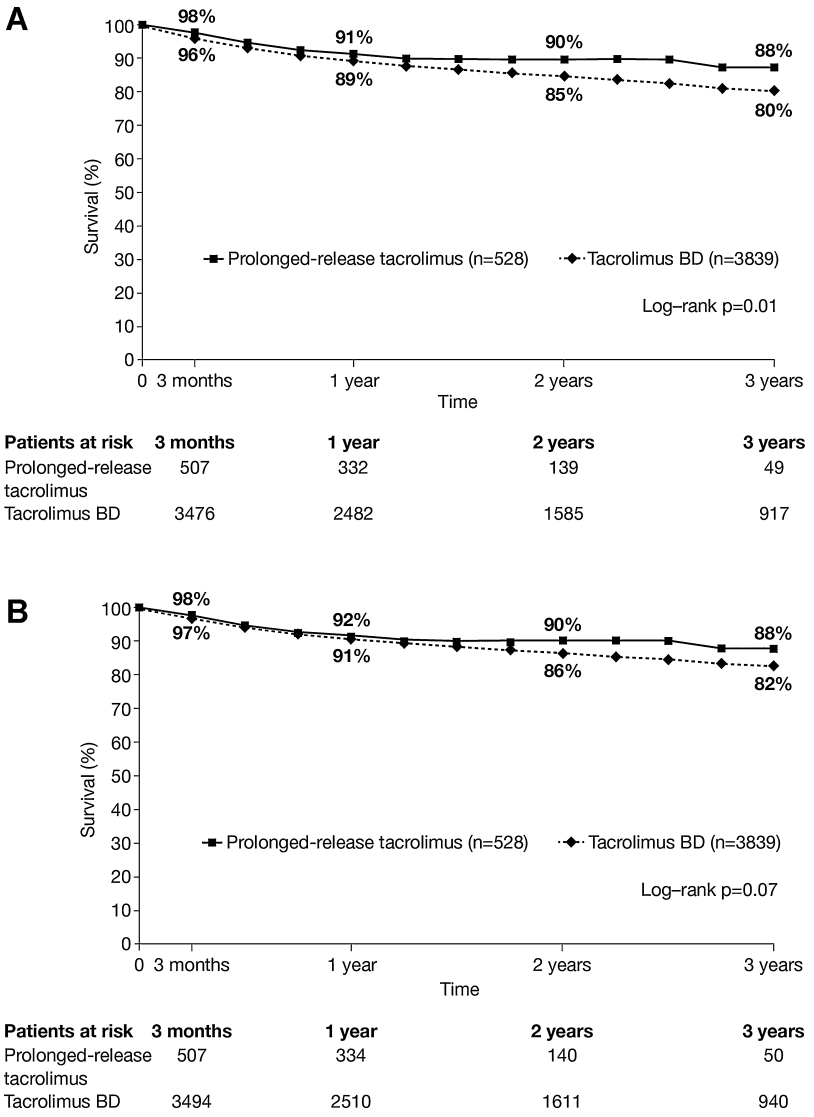

Figure 2: Kaplan–Meier analyses of (A) graft and (B) patient survival over 3 years of treatment with prolonged-release tacrolimus compared with tacrolimus BD after exclusion of patients with < 1 month of follow-up. BD: twice daily.

significant graft survival advantage and a non-significant trend towards an improved patient survival advantage in the prolonged-release tacrolimus versus tacrolimus BD group (8% for graft survival and 6% for patient survival). Kaplan–Meier analyses of the propensity score-matched patients demonstrated a significant graft and patient survival advantage in the prolonged-release tacrolimus versus tacrolimus BD group.

The survival advantages observed in patients treated with prolonged-release tacrolimus versus tacrolimus BD reported in this paper were not observed in short-term, randomized, controlled trials. In the Phase III prolonged-release tacrolimus registration trial, no difference was seen in survival outcomes between prolonged-release tacrolimus and tacrolimus BD over 24 weeks of treatment (26). We hypothesize that differences between the treatment regimens, including probable improved adherence to treatment (18–24) and reduced variability of tacrolimus exposure (15,16) observed with prolonged-release tacrolimus, have long-term beneficial effects. Lieber and colleagues found that non-adherence, as measured by tacrolimus trough variability in the immediate posttransplant setting, was independently associated with graft failure over time (11).

In addition, recent studies have highlighted the importance of low variability in tacrolimus exposure on graft and patient outcomes. Prolonged-release tacrolimus has a more consistent pharmacokinetic (PK) profile than tacrolimus BD, and conversion of patients from tacrolimus BD to prolonged-release tacrolimus has been shown to reduce both intra- and inter-patient variability in tacrolimus trough

Table 4: Univariate analysis of risk factors for reduced graft and patient survival for the propensity score-matched patients

			Graft survival, %			Patient survival, %		
Parameters at first transplant	Category	n	1 year	3 years	p-value[1]	1 year	3 years	p-value[1]
Immunotherapy during Month 1								
Tacrolimus formulation	Prolonged-release tacrolimus	270	95	89	0.002	96	89	0.003
	Tacrolimus BD	540	88	81		89	82	
Initial steroids	No	37	86	82	0.62	86	82	0.54
	Yes	773	91	83		91	84	
Donor characteristics								
Donor sex	Female	333	91	81	0.70	91	81	0.92
	Male	471	90	85		91	86	
Donor age ≥50 years	Yes	420	88	79	0.01	88	79	0.02
	No	361	94	89		94	89	
Donor age ≥60 years	Yes	269	87	77	0.02	88	78	0.03
	No	512	92	87		93	87	
Macro/micro-vesicular graft steatosis	No	122	93	90	0.7	95	92	0.36
	Yes	172	93	87		93	87	
Blood group compatibility	Compatible	34	85	85	0.03	85	85	0.02
	Iso group	758	91	84		92	85	
	Non-compatible	5	80	—		80	—	
Living donor	No	805	90	83	0.66	91	84	0.75
Recipient characteristics								
Recipient sex	Female	265	91	85	0.49	92	85	0.58
	Male	545	90	83		91	84	
Recipient age ≥50 years	Yes	549	89	81	0.08	90	82	0.1
	No	261	93	89		93	89	
Recipient age ≥60 years	Yes	215	89	85	0.91	90	85	0.85
	No	595	91	83		92	84	
Recipient dialysis	No	664	90	85	0.52	91	85	0.44
	Yes	28	88	82		88	82	
Recipient body mass index[2]	Underweight	20	78	78	0.15	78	78	0.19
	Normal weight	363	89	83		90	84	
	Overweight	264	93	87		94	87	
	Obese	128	91	81		92	82	
Recipient viral status								
HBsAg	Negative	717	90	84	0.99	91	84	0.55
	Positive	81	92	83		95	86	
Co-existing HBV and delta virus	Negative	62	88	82	0.88	88	82	0.37
	Positive	10	90	77		100	88	
Anti HCV	Negative	667	91	84	0.58	92	85	0.4
	Positive	143	89	80		89	80	
HIV serology	Negative	809	90	84	0.73	91	84	0.74
	Positive	1	100	—		100	—	
HCV RNA	Negative	116	88	79	0.48	89	80	0.58
	Positive	78	91	81		91	81	
Criteria for liver transplant								
Liver transplant urgency[3]	No	514	91	83	0.77	92	84	0.65
	Yes	48	89	89		89	89	
UNOS status[4]	1	61	88	86	<0.0001	88	86	<0.0001
	2	88	74	72		76	74	
	3	450	93	85		93	85	
	4	211	93	86		94	87	
UNOS status[4] 1 or 2	Yes	149	80	78	<0.0001	81	79	<0.0001
	No	661	93	85		93	86	
MELD score	<14	386	92	83	0.01	93	84	0.01
	14–25	290	91	86		91	87	
	>25	126	84	79		84	80	
Liver function and laboratory values								
Recipient Child–Pugh class	A	157	92	78	0.02	93	79	0.02
	B	172	95	89		95	90	

Table 4: Continued

Parameters at first transplant	Category	n	Graft survival, %			Patient survival, %		
			1 year	3 years	p-value[1]	1 year	3 years	p-value[1]
	C	81	85	74		86	75	
Serum creatinine concentration ≥2 mg/dL	Yes	56	79	74	0.004	79	74	0.002
	No	754	91	84		92	85	
Indication								
Main indication for transplant	Acute liver failure	35	91	78	0.86	91	78	0.71
	Chronic liver disease	523	90	86		92	87	
	Metabolic disease	44	83	83		83	83	
	Tumor (benign)	18	88	88		88	88	
	Tumor (malignant)	180	92	78		92	77	
	Other	10	90	—		90	—	
Acute liver failure as main disease	Yes	35	91	78	0.57	91	78	0.47
	No	775	90	84		91	84	
Cirrhosis as main disease	Yes	452	89	84	0.60	91	85	0.82
	No	358	92	83		92	83	
Cancer as main disease	Yes	180	92	78	0.99	92	77	0.75
	No	630	90	85		91	86	
Milan criteria (in patients with HCC)	Yes	146	94	85	0.01	94	85	0.01
	No	54	86	55		86	54	
HCC with tumor size >50 mm	Yes	14	68	—	0.002	68	—	0.002
	No	191	94	78		94	78	
Surgical procedure								
Total ischemia time	≥12 h	34	90	83	0.86	97	85	0.88
	8–12 h	355	90	84		91	85	
	1–8 h	420	91	83		91	83	
Total ischemia time ≥6 h	Yes	638	89	81	0.01	90	82	0.02
	No	171	94	94		94	94	
Type of graft	Full size	762	90	83	0.87	91	84	0.91
	Domino	11	91	91		91	91	
	Reduced	1	100	—		100	—	
	Split	31	93	93		93	93	
Liver transplant	Heterotopic	5	100	100	0.43	100	100	0.44
	Orthotopic	803	90	83		91	84	

[1]Log-rank p-value.
[2]Body mass index was defined as underweight: <18.5kg/m^2, normal weight: 18.5–24.9kg/m^2, overweight: 25.0–29.9kg/m^2, obesity: ≥30kg/m^2.
[3]Liver transplant urgency was determined by the treating physician and indicated on the questionnaire by a ''yes'' or ''no'' tick box.
[4]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization, 3. Continuous medical care, 4. At home with normal function.
BD: twice daily; HBsAg: HBV surface antigen; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MELD: Model for End-stage Liver Disease; UNOS: United Network for Organ Sharing.

levels (15,16). To put this into context, high intra-patient variability of tacrolimus exposure has been linked with poor clinical outcomes including long-term graft survival (12).

The overall proportion of patients with graft loss was lower in the prolonged-release tacrolimus versus the tacrolimus BD group. While the reasons for graft loss were generally comparable between groups, there was a higher incidence of bacterial infections reported in the prolonged-release tacrolimus versus tacrolimus BD group. This finding contrasts with that of a previous study whereby the rate of infections, including bacterial infections, was comparable between prolonged-release tacrolimus and tacrolimus BD groups (26). In the ELTR analyses, the higher incidence of infections leading to graft loss reported in the prolonged-release tacrolimus group may have been due to more intense immunosuppression, as a larger number of patients in this group received MMF compared with the tacrolimus BD group. This may reflect a more conservative approach by investigators when using a newer immunosuppressive regimen. When the population was matched for the propensity score analyses, the rates of bacterial infection leading to graft loss or mortality over 3 years of treatment were comparable between treatment groups. Interestingly, despite the higher rates of infections, prolonged-release tacrolimus-based immunosuppression was associated with improvements in graft and patient survival versus tacrolimus BD, and this was apparent even at 3 months. When stratified by gender, the incidence of mortality was comparable between groups (data not shown) and both graft and patient

Table 5: Multivariate analyses of risk factors for reduced (A) graft and (B) patient survival for the propensity score-matched patients

Risk factors at first transplant	Risk ratio	95% Confidence interval	p-value
(A) Graft survival (N=810)			
ABO blood group not compatible	6.22	1.30–29.69	0.02
Tacrolimus BD immunotherapy	3.33	1.85–5.99	<0.0001
UNOS status[1] 1 or 2	2.62	1.64–4.19	<0.0001
Total ischemia time of ≥6 h during first liver transplant	2.34	1.16–4.73	0.02
Donor age ≥50 years	1.79	1.12–2.86	0.02
(B) Patient survival (N=810)			
ABO blood group not compatible	6.35	1.32–30.45	0.02
Tacrolimus BD immunotherapy	3.33	1.81–6.12	0.0001
UNOS status[1] 1 or 2	2.53	1.56–4.12	0.0002
Total ischemia time of ≥6 h during first liver transplant	2.09	1.03–4.25	0.04
Donor age ≥50 years	1.72	1.06–2.78	0.03

[1]UNOS status: 1. Hospitalized in the intensive care unit, 2. Continuous hospitalization.
BD: twice daily; UNOS: United Network for Organ Sharing.

survival rates were comparable with previously published data (26,27). Further investigation into the incidence of infection in patients treated with prolonged-release tacrolimus compared with tacrolimus BD would be of interest and should be addressed in future studies.

None of the patients in the prolonged-release tacrolimus group experienced chronic or acute rejection leading to graft loss or mortality compared with a relatively low number of patients in the tacrolimus BD group, although this difference did not reach statistical significance. This is particularly interesting as significantly fewer patients in the prolonged-release tacrolimus versus tacrolimus BD group received corticosteroids at the time of immunosuppression induction.

The majority of data in the field of transplantation are obtained from clinical trials, which represent a relatively specialized and carefully controlled environment, often designed as blinded studies. Postmarketing evaluation is, therefore, important for understanding the natural history of transplant patients and the impact of therapeutic regimens on clinical care. However, the authors recognize that registry data are subject to the limitations of all non-randomized studies. Due to the period in which the data were collected, it is plausible that a proportion of patients in both the prolonged-release tacrolimus and tacrolimus BD groups were enrolled in clinical trials. This may have introduced a bias in terms of patient selection, which due to the difference in the number of patients in the treatment groups could have had a greater impact on outcomes for the prolonged-release tacrolimus group. Also, as with many registry analyses, follow-up may be less aggressive than in the context of clinical trials and there is, therefore, a limit to how much patient information is available at all time points. It should also be noted that the questionnaire used by the registry specifies prolonged-release tacrolimus as one of the immunosuppressive agents; it does not, however, distinguish between Prograf™ (Astellas Pharma Europe Ltd., UK) and generic tacrolimus in the tacrolimus BD group. However, based on the period over which the data were collected, the use of generic tacrolimus would have been limited to a small number of centers. A further limitation of the study is that there was an imbalance between the numbers of patients in the two groups. To control for this difference, univariate and multivariate analyses using propensity score-matched patients were performed; these analyses confirmed that tacrolimus BD was an independent risk factor for reduced long-term graft and patient survival. However, as propensity-score matching can only be used to balance measured variables, it is not possible to completely exclude residual imbalances for unmeasured or unknown variables. In addition, the tacrolimus dose and/or exposure over time were not recorded in the registry questionnaire and there is limited information available on concomitant medications of the patients throughout the study. Furthermore, although this is a European registry, the questionnaire does not include ethnicity. There were some differences in baseline characteristics between the two treatment groups, including recipient age, recipient HIV, HCV and HCC status, and concomitant immunosuppression, which may have impacted on long-term outcomes. However, univariate and multivariate analyses on the propensity score-matched population, with more balanced baseline characteristics, confirmed that tacrolimus BD was an independent risk factor for reduced long-term graft and patient survival. To ascertain the effect of the time of transplant, date of transplant was included as a categorical and again as a dichotomic variable in the multivariate analysis (data not shown). In both analyses, time of entry to the study was not identified as a significant risk factor for reduced graft or patient survival.

All analyses in this study were performed retrospectively on the population that excluded patients with <1 month of follow-up. This approach was used to minimize the impact of early confounding factors, such as graft loss related to surgical procedures, on the final outcomes. Treatment groups were stratified by prolonged-release tacrolimus or tacrolimus BD therapy at Month 1 and patients remained in

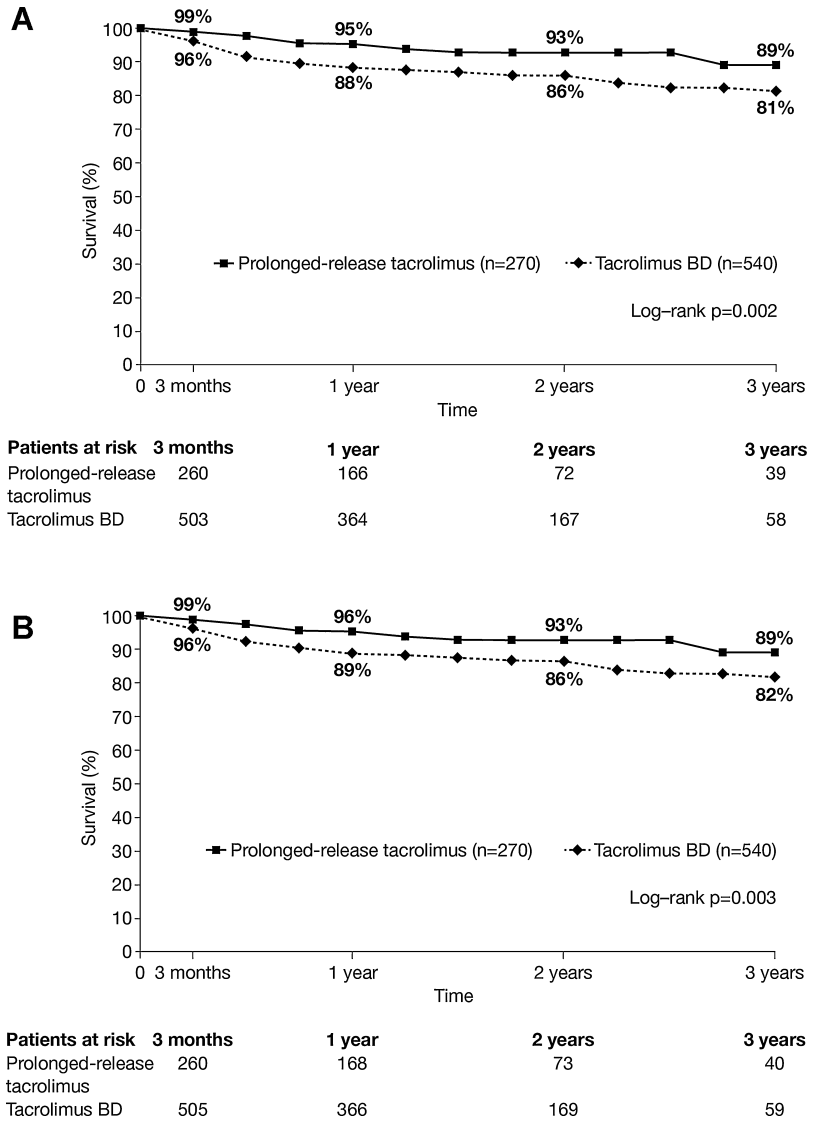

Figure 3: Kaplan–Meier analyses of (A) graft and (B) patient survival over 3 years of treatment in with prolonged-release tacrolimus compared with tacrolimus BD for the propensity score-matched patients. BD, twice daily.

these allocated groups regardless of whether or not a change of immunosuppressive therapy occurred after Month 1.

Although this was a European study where transplantation procedures and aftercare were predominantly state-funded, and were not covered by private healthcare insurance, potential socioeconomic differences between treatment groups could not be excluded as this information is not available in the ELTR database. In an attempt to control for this, only clinics who used both tacrolimus BD and prolonged-release tacrolimus were included in these analyses. In the univariate and multivariate analyses, where the centers were included as a categorical variable (and repeated as a dichotomic variable), the centers were not found to be an independent predictor of graft or patient survival.

Owing to the multiple factors influencing the outcomes of patients after liver transplantation, a study demonstrating that an immunosuppressive drug (administered as induction therapy) may independently impact graft and patient survival, suggesting that there is a significant long-term improvement provided by prolonged-release tacrolimus- versus tacrolimus BD-based immunosuppression (risk ratio: 1.81, $p = 0.001$; 1.72, $p = 0.004$ for graft and patient survival, respectively). Despite the fact that steps have been taken to minimize the risk of bias, the effect of residual confounders cannot be excluded. Additional analyses as more patients reach 3 years of treatment in the ELTR, and

Table 6: Causes of graft loss and mortality over 3 years of treatment

		Graft loss, n (%)				Mortality, n (%)			
Category	Type	All (N=4367)	Prolonged-release tacrolimus (n=528)	Tacrolimus BD (n=3839)	p-value[1]	All (N=4367)	Prolonged-release tacrolimus (n=528)	Tacrolimus BD (n=3839)	p-value[1]
Overall		556	47	509		478	45	433	
Technical complications	All	71 (12.77)	5 (10.64)	66 (12.97)	0.65	25 (5.23)	3 (6.67)	22 (5.08)	0.65
	Biliary	29 (5.22)	3 (6.38)	26 (5.11)	0.71	12 (2.51)	1 (2.22)	11 (2.54)	0.90
	Hemorrhage	4 (0.72)	0	4 (0.79)	0.54	4 (0.84)	0	4 (0.92)	0.52
	Vascular	39 (7.01)	2 (4.26)	37 (7.27)	0.44	9 (1.88)	2 (4.44)	7 (1.62)	0.18
	Hepatic infarction	1 (0.18)	0	1 (0.20)	0.76	1 (0.21)	0	1 (0.23)	0.75
Rejection	All	13 (2.34)	0	13 (2.55)	0.27	7 (1.46)	0	7 (1.62)	0.39
	Acute	3 (0.54)	0	3 (0.59)	0.60	2 (0.42)	0	2 (0.46)	0.65
	Chronic	10 (1.80)	0	10 (1.96)	0.33	5 (1.05)	0	5 (1.15)	0.47
Non-tumoral recurrence		61 (10.97)	5 (10.64)	56 (11.00)	0.94	47 (9.83)	5 (11.11)	42 (9.70)	0.76
Other liver complications		35 (6.29)	3 (6.38)	32 (6.29)	0.98	25 (5.23)	3 (6.67)	22 (5.08)	0.65
Tumor	Tumor recurrence	73 (13.13)	6 (12.77)	67 (13.16)	0.94	72 (15.06)	6 (13.33)	66 (15.24)	0.73
	De novo tumor	33 (5.94)	2 (4.26)	31 (6.09)	0.61	33 (6.90)	2 (4.44)	31 (7.16)	0.49
	De novo tumor (lymph)	7 (1.26)	0	7 (1.38)	0.42	7 (1.46)	0	7 (1.62)	0.39
Infection	Overall	160 (28.78)	27 (57.45)	133 (26.13)	<0.0001	156 (32.64)	26 (57.78)	130 (30.02)	0.0002
	Bacterial	91 (16.37)	19 (40.43)	72 (14.15)	<0.0001	88 (18.41)	18 (40.00)	70 (16.17)	<0.0001
	Viral	6 (1.08)	1 (2.13)	5 (0.98)	0.47	6 (1.26)	1 (2.22)	5 (1.15)	0.54
	Fungal	22 (3.96)	1 (2.13)	21 (4.13)	0.50	21 (4.39)	1 (2.22)	20 (4.62)	0.46
	Undefined	51 (9.17)	7 (14.89)	44 (8.64)	0.16	49 (10.25)	6 (13.33)	43 (9.93)	0.47
General	Gastrointestinal	18 (3.24)	3 (6.38)	15 (2.95)	0.20	17 (3.56)	3 (6.67)	14 (3.23)	0.24
	Cardiovascular	38 (6.83)	1 (2.13)	37 (7.27)	0.18	38 (7.95)	1 (2.22)	37 (8.55)	0.14
	Cerebrovascular	14 (2.52)	1 (2.13)	13 (2.55)	0.86	14 (2.93)	1 (2.22)	13 (3.00)	0.77
	Renal	9 (1.62)	2 (4.26)	7 (1.38)	0.13	9 (1.88)	2 (4.44)	7 (1.62)	0.18
	Pulmonary	37 (6.65)	3 (6.38)	34 (6.68)	0.94	37 (7.74)	3 (6.67)	34 (7.85)	0.78
	Multiple organ failure	23 (4.14)	0	23 (4.52)	0.14	23 (4.81)	0	23 (5.31)	0.11
Other		44 (7.91)	2 (4.26)	42 (8.25)	0.33	41 (8.58)	2 (4.44)	39 (9.01)	0.30
Social cause		3 (0.54)	0	3 (0.59)	0.60	3 (0.63)	0	3 (0.69)	0.58
Suicide		2 (0.36)	0	2 (0.39)	0.67	2 (0.42)	0	2 (0.46)	0.65

[1]P-value Mantel–Haenszel Chi-Square between treatment cohort comparisons; BD: twice daily.
Data are presented for up to three causes of graft loss or patient mortality for each patient.

analyses from other registries of primary liver transplant recipients are, therefore, required to further validate the differences between prolonged-release tacrolimus and tacrolimus BD and to put these data into context.

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Disclosure

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