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REVIEW ARTICLE

Conversion from Extended-Dose-Release Tacrolimus to Melt-Dose Tacrolimus in High Metabolizer Patients: Is the New Formulation of LPCT the Best Option for High Metabolizer Kidney Transplanted Patients?

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Abstract

Tacrolimus (FK506) is the most widely used anti-rejection drug in kidney transplantation, especially its extended release Tacrolimus formulation (ER-Tac, Advagraf), which is used when target blood levels can be difficult to reach in high metabolizer patients. In this retrospective monocentric study, we analyzed the effect of a switch from ER-Tac to LifeCycle Pharma Tacrolimus (LPCT, Envarsus) on the dose/level ratio of FK506 in high metabolizer patients that cannot achieve target blood levels in the first 6 months after transplantation. We observed a statistically significant improvement in the level to dose ratio after the switch. Renal function remained stable. We also observed a reduction in the development of tremors. Our data suggest that LPCT can be used in a safer way in high metabolizer kidney transplant recipients.

Keywords: kidney transplantation; extended-dose-release Tacrolimus; melt-dose Tacrolimus; renal function; tremors; high metabolizer recipients

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Introduction

Tacrolimus (FK506) is the most widely used immunosuppressive drug in kidney transplant patients for preventing graft rejection. However, it has a narrow therapeutic range and requires close monitoring. In fact, blood concentration below the therapeutic range is associated with increased risk of rejection, whereas blood concentration over the therapeutic range increases the risk of toxicity and side effects (anticalcineurinc nephrotoxicity, infections, diabetes, BK virus nephropathy, tremor). Various formulations of FK506 are currently available: immediate-release Tacrolimus formulations (IR-Tac), extended-release tacrolimus formulations (ER-Tac), and LifeCycle Pharma Tacrolimus (LCPT). Twice-daily IR-Tac (Prograf®, Astellas Pharma, or the generic formulation) was the first produced formulation, and it is administered every 12 h. The second produced formulation

was ER-Tac (Advagraf®, Astellas Pharma), and it allowed once-daily administration. A new, once-daily ER-Tac (LCPT: Envarsus®, Chiesi Farmaceutici) was released recently. It was designed with a Melt-Dose technology, with the aim to increase the bioavailability of the drug with low water solubility. LCPT releases the drug in a controlled manner at a predetermined rate, duration, and location in the gastrointestinal tract to achieve and maintain a more stable therapeutic blood concentration of FK506 (1). Patients with FK506's administered dose and level ratio > 1 are defined as high metabolizers. In these patients, achieving target blood levels of immunosuppressants can be particularly difficult, and it represents a recurring challenge for physicians. This is particularly important in the first months after transplantation when the risk of acute rejection is higher. The aim of our retrospective observational study was to analyze the effects of a switch from ER-Tac to LCPT on bllod tacrolimus trhough levels and on dose to level ratio in high metabolizer kidney transplant recipients who did not achieve optimal blood levels of tacrolimus.

Methods

We selected 10 patients who received kidney transplantation in our institution and were switched from ER-Tac to LCPT in the first 6 months after transplantation because of difficulty in reaching target tacrolimus blood levels (8–12 ng/mL in the first 6 months after surgery) in spite of a continuous increase in oral daily dose of Tacrolimus. The treatment switch was decided by the nephrologists in charge of the patients. The dose of LPCT was calculated as the 70% of the the dose of ER-TAC at the time of the switch, as recommended by the manufacter.

In this analysis, we compared FK 506 blood levels, serum creatinine, dose to level ratio, glycemia, ER-Tac, and LCPT doses at time of switch, after 1 week, and after 1 month. Morevorer, we wanted to observe whether an improvement or a disappearance of tremors occurred after the treatment switch. Statistical analysis included Student *t*-test for unpaired groups. Statistical analysis was performed using SPSS® software.

Table 1. In the left colon parameters are presented at the time of the switch (t0) and after 1 month (t1)

	Media ± SD	HR (95% CI)			P
		Inferior	Superior	T	
Creatinine T0 (mg/dL)	2.10 ± 1.44	−0.28	1.24	1.44	0.188
Creatinine T1 (mg/dL)	1.62 ± 0.57				
Azotemia T0 (mg/dL)	0.75 ± 0.69	−0.29	0.62	0.83	0.427
Azotemia T1 (mg/dL)	0.58 ± 0.27				
Proteinuria T0 (gr/24h)	0.56 ± 0.55	0.11	0.34	4.75	***0.001***
Proteinuria T1 (gr/24h)	0.33 ± 0.55				
Glycemia T0 (mg/dL)	90.89 ± 8.89	−16.21	1.54	−1.90	0.093
Glycemia T1 (mg/dL)	98.22 ± 15.50				
Cholesterol T0 (mg/dL)	202.63 ± 59.13	−18.25	25.75	0.40	0.69
Cholesterol T1 (mg/dL)	198.88 ± 47.05				
Fk levels T0 (ng/mL)	9.82 ± 3.39	−2.38	1.45	−0.56	0.59
Fk levels T1 (ng/mL)	10.28 ± 3.79				
Fk dose T0 (mg/day)	16.44 ± 5.38	2.36	8.46	4.09	***0.003***
Fk dose T1 (mg/day)	11.02 ± 6.20				
Fk dose/level T0	2.94 ± 1.16	1.09	2.36	6.27	***0.0001***
Fk dose/level T1	1.21 ± 0.84				

In the P value colomn statistically significant values are expressed in bold character.

Results

We selected 10 patients, as explained above, and their data are summarized in Table 1. After the switch from ER-Tac to LCPT, we observed a reduction of FK506 dose (16.44 ± 5.38 vs 11.02 ± 6.20; P = 0.003) and a reduction of FK506 dose/level ratio (2.94 ± 1.16 vs 1.21 ± 0.84; P = 0.0001). Renal function ad serum creatinine remained stable (2.10 ± 1.44 vs 1.62 ± 0.57; P = 0.188). We did not observe any other variation in the parameters that we evaluated. All patients reported improvement in tremors, confirming a partial or total disappearance of the tremors.

Discussions

Our study shows how LCPT formulation allows to increase FK 506 blood levels in high metabolizer patients who did not reach therapeutical Tacrolimus levels with ER-Tac in the first 6 months after kidney transplantation. These data have been confirmed by many other authors. Tremblay et al. (2) compared all three innovator formulations of Tacrolimus (IR-Tac, ER-Tac, LCPT). A conversion factor of 1:1:0.80 for IR-Tac:ER-Tac:LCPT was used. The median total daily dose was similar for IR-Tac and ER-Tac and lower for LCPT. Significantly higher exposure on a per milligram basis, lower intraday fluctuation, and prolonged time to peak concentration were found for LCPT versus IR-Tac or ER-Tac. LCPT formulations would allow greater flexibility in the timing of blood draws for tacrolimus concentrations. Philosophe et al. (1) found that blood concentrations taken at both 21 and 27 h post-dose were highly correlated with area under the concentration–time curve over 24 h AUC. The high correlation coefficients found in this study were similar to those found by Gaber et al. (3) in a phase 2 study of stable adult kidney transplant patients on IR-Tac who were converted to LCPT. LCPT has greater bioavailability, a steadier and more consistent concentration–time profile over 24 h, and reduced peak-to-trough fluctuations and swing compared with IR-Tac. Bunnapradist et al. (4) demonstrated that LCPT has comparable efficacy and improved tolerability compared with IR-Tac. They reported lower treatment failure rates (death, graft failure, biopsy-proven acute rejection, or lost to follow-up) associated with LCPT among high-risk patients, such as black kidney transplant recipients and kidney transplant recipients aged above 65 years (5). Trofe-Clark et al. compared the pharmacokinetics of IR-Tac and LCPT in African American patients. The CYP3A5*1 allele, preponderant in African Americans, is a polymorphism in CYP3A5 genes that is associated with rapid metabolism, subtherapeutic concentrations, and higher dose requirements for tacrolimus, all contributing to worse outcomes. They observed that therapeutic tacrolimus trough concentrations were achieved with IR-Tac in most African Americans, with significantly higher peak concentrations, potentially magnifying the risk for toxicity and adverse outcomes. This pharmacogenetic effect was attenuated by delayed tacrolimus absorption with LCPT (6). In addition, in our case study, we observed a similar rate of renal function and an improvement in the development of tremors after a switch from ER-TAC to LCPT. Tremor is a common tacrolimus treatment side effect, and it is correlated with peak-dose drug concentration. LCPT formulations have a reduced maximum blood concentration (Cmax) with comparable AUC exposure. All patients enrolled in our study reported an improvement in tremor after the switch. Langone et al. enrolled 38 kidney transplant recipients with a reported clinically significant tremor and switched them to LCPT. A statistically and clinically significant improvement in tremor resulted after the pharmacological conversion (7). Finally, we can also observe a reduction in costs due to the fact that target blood levels were achieved with a lower drug dose.

It is necessary to point out some limitations of our study; in particular, we underline that this is a retrospective monocentric small study, and the patient selection was not performed following a protocol but was decided by physicians on their clinical interpretation. In spite of the shortcomings, our data suggest that LCPT can be used in a safer way in high metabolizer kidney transplant recipients.

Conclusions

LCPT formulations have demonstrated noninferiority, similar safety, improved bioavailability, a consistent concentration time profile, and less peak and peak-trough fluctuations compared to other formulations. Also, our data express a better FK506 dose to level ratio and a reduction of tremors after the switch to LCPT. Further randomized studies on larger populations are needed to confirm the effective advantages of the switch from IR-Tac and ER-Tac to LCPT.

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