MeltDose Technology vs Once-Daily Prolonged Release Tacrolimus in De Novo Liver Transplant Recipients

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ABSTRACT

Background. An extended-release formulation of tacrolimus designed for once-daily administration (LCP-TAC) is a new prolonged-release tacrolimus (TAC-PR) formulation using a drug delivery technology designed to enhance the bioavailability of drugs compared with TAC-PR. The aim of this study was to retrospectively compare de novo administration of LCP-TAC and TAC-PR for therapeutic trough levels and daily dosage during the first 30 days after first liver transplant (LT).

Methods. A total of 35 patients submitted to first LT between 2016 and 2018 were retrospectively enrolled: 16 received LCP-TAC, while 19 received TAC-PR as de novo immunosuppression. Patients were analyzed for daily dosage and trough levels at postoperative days (PODs) 3, 7, 15, and 30.

Results. The initial dose of tacrolimus did not differ between LCP-TAC and TAC-PR (mean, 5.19 [SD, 1.72] mg/d vs mean, 5.26 [SD, 1.91] mg/d, $P = .90$). On PODs 7, 15, and 30 the daily dosage was statistically lower for LCP-TAC compared with TAC-PR (mean, 5.44 [SD, 2.06] mg/d vs mean, 7.68 [SD, 2.91] mg/d, $P = .01$; mean, 5.33 [SD, 2.23] mg/d vs mean, 8.82 [SD, 2.35] mg/d, $P < .001$; and mean, 5.38 [SD, 2.50] mg/d vs mean, 9.81 [SD, 3.78] mg/d, $P < .001$, respectively). The therapeutic trough levels were significantly higher for LCP-TAC on POD 3 (mean, 5.05 [SD, 3.58] ng/mL vs mean, 2.42 [SD, 2.75] ng/mL, $P = .03$) and POD 5 (mean, 7.35 [SD, 5.12] ng/mL vs mean, 4.17 [SD, 2.05] ng/mL, $P = .04$), while no differences were found on PODs 7, 15, and 30.The percentage of patients on POD 3 achieving a trough level higher than 6 ng/mL was higher for LCP-TAC than TAC-PR (40% vs 13%, $P = .05$).

Conclusions. LCP-TAC after LT is safe and might enhance bioavailability, reducing the amount of drug necessary to achieve therapeutic trough levels compared with TAC-PR.

TACROLIMUS is a mainstay of immunosuppression in organ transplantation and it is characterized by an immediate release formulation requiring a twice-daily dose regimen. One of the hazards related to immediate-release tacrolimus (TAC-IR) is the poor and heterogeneous bioavailability [1]. Maximum drug concentration and area under the curve are critical parameters to determinate an adequate immunosuppression. Deviation from targeted therapeutic regimen may cause adverse effects that can potentially compromise both recipients and graft outcome. Recipients adherence to therapy prescriptions seems to be negatively influenced by dose fractioning of the drug, that is, the higher the dose fractionation, the lower is the adherence [2]. Therefore, a new tacrolimus formulation with a prolonged-release (TAC-PR) capsules and a single daily dose administration was developed, resulting in increased

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Table 1. Clinical and Demographic Characteristics of the Study Population, Details of Tacrolimus Dosage, and Trough Level at Different Points After Liver Transplant

	LCP-TAC Group (n = 16)	TAC-PR Group (n = 19)	*P* Value
Recipient age, mean (SD), y	59 (9)	59 (8)	.88
Recipient male-to-female ratio	11/5	16/3	.27
MELD at liver transplant, mean (SD)	19 (9)	16 (6)	.37
HCC diagnosis, %	50	47	.89
Donor age, mean (SD), y	51 (17)	62 (13)	.07
Initial tacrolimus dosage, mean (SD), mg/d	5.19 (1.72)	5.26 (1.91)	.90
POD 3 tacrolimus dosage, mean (SD), mg/d	4.91 (2.1)	5.17 (1.92)	.70
POD 3 tacrolimus trough level, mean (SD), ng/mL	5.05 (3.58)	2.42 (2.75)	.03*
POD 5 tacrolimus dosage, mean (SD), mg/d	4.97 (2.21)	6.33 (2.35)	.09
POD 5 tacrolimus trough level, mean (SD), ng/mL	7.35 (5.12)	4.17 (2.05)	.03*
POD 7 tacrolimus dosage, mean (SD), mg/d	5.44 (2.06)	7.68 (2.91)	.01*
POD 7 tacrolimus trough level, mean (SD), ng/mL	8.03 (5.44)	6.06 (3.03)	.21
POD 15 tacrolimus dosage, mean (SD), mg/d	5.33 (2.23)	8.82 (2.35)	<.01*
POD 15 tacrolimus trough level, mean (SD), ng/mL	8.62 (7.86)	6.69 (2.71)	.36
POD 30 tacrolimus dosage, mean (SD), mg/d	5.38 (2.50)	9.81 (3.78)	<.01*
POD 30 tacrolimus trough level, mean (SD), ng/mL	9.10 (5.78)	7.96 (4.16)	.54

HCC, hepatocellular carcinoma; LCP-TAC, extended-release formulation of tacrolimus designed for once-daily administration; MELD, Model for End-Stage Liver Disease; POD, postoperative day; TAC-PR, prolonged-release tacrolimus.
*$P < .05$.

adherence to therapy compared with a twice-daily schedule [3]. However, this new formulation did not solve the problem of interindividual and intraindividual variability, usually resulting in lesser bioavailability. Nanotechnology and nanoformulations provided effective tools for overcoming the issue of poor bioavailability by virtue of the nanosize of drugs [4]. MeltDose technology, a platform developed by Veloxis Pharmaceuticals A/S (Hørsholm, Denmark), is a drug delivery technology used to enhance the oral bioavailability and control the release of a drug, especially low water-soluble or insoluble drugs. Particle size plays a vital role in bioavailability since smaller particle size enables better dissolution and absorption. Unlike conventional and nanocrystal drug delivery formulations, which use larger particles that are more difficult to absorb, with MeltDose technology the particles of the active substance have been reduced as small as possible down to single molecules, passing from the size of 10 mm of the conventional drug to a solution ≤ 0.1 mm diameter to be organized into oral tablets [5]. An extended-release formulation of TAC designed for once-daily administration (LCP-TAC) is a new TAC-PR formulation. The aim of this study was to retrospectively compare de novo administration of LCP-TAC and TAC-PR in terms of therapeutic trough levels and daily dosage during the first 30 days after first liver transplant (LT).

PATIENTS AND METHODS

A total of 35 patients submitted to first LT between 2016 and 2018 at the Liver Transplant Center of Udine, Italy, were retrospectively enrolled; LCP-TAC (Envarsus) was used as de novo immunosuppression in 16 cases (LCP-TAC group), while 19 received TAC-PR (Advagraf) (TAC-PR group). Both groups received an intraoperative bolus of steroids (500 mg) tapered to 25 mg daily on postoperative day (POD) 5 and maintained until POD 30. Mofetil mycophenolate was not used in any patient during the considered post-LT time frame. Demographic and clinical data of donors and recipients were reviewed from the local electronic database. Initial daily dosage (mg/d) and dose at PODs 3, 7, 15, and 30 were retrospectively recorded from chart review; predose trough levels (ng/mL) were analyzed at the same time points and compared between groups. The daily dosage of tacrolimus was analyzed as total daily dose (mg/d) given to the patient and also normalized for patient's weight (mg/kg) in both groups. Categorical variables and frequencies were expressed by percentage, while continuous variables were expressed by mean (SD) or median (range), as appropriate. For categorical variables, cross-tabulations were generated, and χ^2 or Fisher exact test was used to compare distributions. For continuous variables *t* test or Mann-Whitney test was used. A *P* value less than .05 was considered significant.

RESULTS

No significant differences were found between groups in terms of recipient and donor characteristics: recipient age at LT, recipient sex, Model for End-Stage Liver Disease at LT, hepatocellular carcinoma diagnosis, and donor age (Table 1). The most frequent etiology of liver disease was alcoholic in both groups (50% and 47%, $P = .90$) followed by hepatitis C virus infection (31% vs 42%, $P = .53$), without any significant difference. The initial dose of tacrolimus did not differ between LCP-TAC and TAC-PR (mean, 5.19 [SD, 1.72] mg/d vs mean, 5.26 [SD, 1.91] mg/d, $P = .90$). Subsequently, tacrolimus daily dosage remained similar on PODs 3 and 5, while on PODs 7, 15, and 30 the daily dosage was statistically lower for LCP-TAC compared with TAC-PR (Table 1). The daily dosage of tacrolimus normalized for patient's weight confirmed a lower quantity of LCP-TAC compared with TAC-PR only at PODs 15 and 30, while no statistically significant differences were found at earlier time points. The therapeutic trough levels were significantly higher for LCP-TAC on POD 3 (mean, 5.05 [SD, 3.58] ng/mL vs mean, 2.42 [SD,

2.75] ng/mL, $P = .03$) and POD 5 (mean, 7.35 [SD, 5.12] ng/mL vs mean, 4.17 [SD, 2.05] ng/mL, $P = .04$), while no differences were found on PODs 7, 15, and 30. The percentage of patients achieving a trough level higher than 6 ng/mL at the considered time points was 40% vs 13% ($P = .05$) on POD 3, 47% vs 25% ($P = .15$) on POD 5, 69% vs 44% ($P = .12$) on POD 7, 69% vs 61% ($P = .73$) on POD 15, and 71% vs 81% ($P = .781$) on POD 30 for LCP-TAC and TAC-PR, respectively, confirming that LCP-TAC achieved therapeutic trough levels earlier than TAC-PR despite a 25% lower median dose of drug administered during the first month after LT. No episodes of acute cellular rejection were registered during the study period.

DISCUSSION

TAC is a calcineurin inhibitor much more potent than cyclosporine, but its bioavailability is low and variable, often creating problems of clinical efficacy. The LCP-TAC uses a MeltDose technology and represents an innovation in the field of the immunosuppressive drugs. This new technology increases the amount of active ingredient that reaches the blood, ensuring higher therapeutic efficacy. In a phase 2 study conducted on stable LT patients [6], pharmacokinetic data demonstrated consistent exposure at lower conversion dose. The Cmax, Cmax/Cmin ratio, percent fluctuation, and swing were significantly lower ($P < .001$), and Tmax was significantly lower ($P < .001$) for LCP-TAC vs TAC-IR. In 2014, Grinyo et al [7] reported that the adjusted 1-year cumulative dose was statistically reduced for LCP-TAC compared with TAC-IR. The authors concluded that LCP-TAC significantly reduces the number of doses in the short and long term, with significant cost savings. Altieri et al [8] published an observational study including 44 stable LT patients (median delay after LT of 72.5 months) converted from TAC-PR to LCP-TAC based on a 1:0.70 proportion. Mean dose of tacrolimus was 2.65 (SD, 1.24) mg/d before conversion and 2.09 (SD, 1.68) mg/d after conversion ($P < .05$), with ratio of 1:0.79. Mean serum tacrolimus trough level increased after conversion but returned to the initial preconversion level as well as administered dosage after 6 months. The authors concluded that conversion from prolonged-release to extended-release tacrolimus in stable LT patients is safe and cost-effective under careful monitoring. In this study we retrospectively compared LCP-TAC vs TAC-PR in de novo LT recipients, focusing on administered daily dose and therapeutic trough levels during the first 30 days after transplant. LCP-TAC resulted in faster achievement of therapeutic trough levels despite no difference in the amount of drug delivered. Moreover, after stabilization of tacrolimus blood levels, patients given LCP-TAC required a 25% lower median dose of administered drug to maintain the same therapeutic trough level compared with TAC-PR. To the our knowledge this is the first study, although retrospective and with limited numbers, reporting the use of LCP-TAC immediately after LT and showing that tacrolimus given by MeltDose technology might enhance bioavailability and reduce the amount of drug that should be administered to achieve therapeutic trough levels when compared with TAC-PR in de novo liver transplant recipients.

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