Abstract

Objectives: After organ transplant, strategies to simplify the therapeutic regimen may improve adherence and prevent rejection and/or graft loss. The aim of the present study was to evaluate the safety of conversion from once-daily prolonged-release tacrolimus (Advagraf; Astellas Pharma Europe Limited, Middlesex, UK) to once-daily extended-release tacrolimus (Envarsus; Chiesi SAS, Nanterre, France) in stable adult liver transplant recipients.

Materials and Methods: This observational study included 44 liver transplant patients (median age of 59 y; 63.6% men; median delay after transplant of 72.5 mo). Conversion was based on a 1:0.70 proportion.

Results: Mean dose of tacrolimus was 2.65 ± 1.24 mg/day before conversion and 2.09 ± 1.68 mg/day after conversion (P < .05), with ratio of 1:0.79. Mean serum tacrolimus trough level increased after conversion (4.92 ± 1.65 vs 5.60 ± 2.89 ng/mL; P < .05), with ratio of 1:1.14. Six months after conversion, mean dose of tacrolimus was 1.65 ± 0.93 mg/day (ratio of 1:0.62) and mean serum tacrolimus trough level was 4.82 ± 1.85 ng/mL, similar to the initial level before conversion. At the end of follow-up, 2 patients had returned to once-daily prolonged-release tacrolimus because of adverse effects (allergy, digestive trouble), which resolved thereafter. The mean cost of tacrolimus therapy was 5.54 ± 2.29 Euros/patient/day before conversion and 4.11 ± 2.32 Euros/patient/day after conversion (P < .05).

Conclusions: Conversion from prolonged-release to extended-release tacrolimus in stable liver transplant patients is safe and cost-effective; however, initially, dose adaptations and careful monitoring are required.

Key words: Cost, Liver transplantation, Outcome, Pharmacokinetics

Introduction

Immunosuppressive regimens after liver transplant (LT) are based on a calcineurin inhibitor, (either cyclosporine or tacrolimus). Tacrolimus became first available as an immediate-release formulation (IR-Tac) administered twice daily (Prograf; Astellas Pharma Europe Limited, Middlesex, UK). Two formulations of tacrolimus have been developed to be administered once daily: a prolonged-release (PR-Tac) formulation (Advagraf; Astellas Pharma Europe Limited) and more recently an extended-release (ER-Tac) formulation (Envarsus; Chiesi SAS, Nanterre, France).

Conversion from twice-daily to once-daily tacrolimus has been studied in maintenance LT recipients, using either PR-Tac or ER-Tac. These studies demonstrated that pharmacokinetics of twice-daily tacrolimus and the 2 formulations of once-daily tacrolimus are significantly different. Because no such data are available to date, the aim of the present study was to analyze the impact of conversion in daily practice from PR-Tac to ER-Tac among a large cohort of stable LT recipients, especially with regard to pharmacokinetics, safety, and cost.

Materials and Methods

Study design

This was a single center study conducted in adult LT patients. We performed a retrospective analysis of our cohort of patients, based on prospectively
recorded clinical charts. Inclusion criteria were as follows: at least 6 months of posttransplant follow-up and no acute rejection episodes in the previous 3 months. Conversion from PR-Tac to ER-Tac was based on a 1:0.7 proportion (but eventually adapted to available formulations of ER-Tac; i.e., 0.75, 1, and 4 mg) and then modified on the basis of serum levels or adverse effects. Tacrolimus was taken in the morning, 1 hour before or 2 hours after breakfast, as recommended by the manufacturers. Doses and serum trough levels of tacrolimus and liver and renal function were recorded on the day of conversion, every 2 weeks for 2 months, and at 3 and 6 months after conversion (serum trough level was recorded usually every 3-6 months in maintenance patients before conversion). In addition, rejection episodes, arterial hypertension, dyslipidemia, and diabetes mellitus were assessed during the routine follow-up. Adverse effects were also recorded.

Conversion was performed after patients gave their informed consent (both formulations are approved in France). The aim of conversion was to reduce the cost of tacrolimus therapy, according to the French Public Health recommendations. Cost of tacrolimus therapy was based on the French official cost as of July 2016 (62.90 Euros for 30 × 1 mg for Advagraf and 74.79 Euros for 30 × 1 mg for Envarsus).

Renal function was measured as glomerular filtration rate, estimated by the simplified Modification of Diet in Renal Disease formula. Arterial hypertension was defined as blood pressure > 140/90 mm Hg at the 2 following visits or when an antihypertension treatment was used. Dyslipidemia was defined as hypercholesterolemia > 220 mg/dL and hypertriglyceridemia > 200 mg/dL at the 2 following visits or when a hypolipidemic treatment was used. Diabetes mellitus was defined as fasting plasma glucose > 126 mg/dL at the 2 following visits or when a hypoglycemic treatment was used. Rejection was defined according to the BANFF criteria on liver biopsy.

Statistical analyses
Quantitative variables were described using mean, median, range, and standard deviation. Categorical values were tabulated, and percentages were calculated. Quantitative variables were compared using t test (for repeated measures) and considered significant at \( P < .05 \).

Results

Characteristics of the study population
Between October 2015 and November 2015, 44 patients (28 men and 16 women) with median age of 59 years (range, 37-74 y) were enrolled in the study after a median interval of 72.5 months (range, 6-333 months) after LT. Alcoholic cirrhosis was the main indication for LT. Immunosuppressive therapy at the time of conversion consisted of tacrolimus alone in 20 patients or tacrolimus with mycophenolate mofetil in 24 patients (with steroids in 4 patients). Preconversion mean tacrolimus trough level was 4.92 ± 1.65 ng/mL, with a daily dose of 2.65 ± 1.24 mg. Patient characteristics are summarized in Table 1. To the best of our knowledge, patients were not taking drugs that could interact with tacrolimus.

| Table 1. Patient Characteristics at Time of Conversion |
|---------------------------------|-----------------|
| Characteristic (N = 44 Patients) | Median (Range) or No. (%) |
| Male/female                     | 28/16           |
| Age at conversion, y            | 59.0 (37-74)    |
| Body mass index at conversion, kg/m² | 27.1 (22.1-42.3) |
| Time from transplant to conversion, mo | 72.5 (6-333)    |
| Indication for liver transplant |                 |
| Alcohol                         | 30 (68.2%)     |
| Hepatitis C or hepatitis B virus | 7 (15.9%)      |
| Autoimmune liver disease        | 5 (11.4%)      |
| Other                           | 2 (4.5%)       |
| Comorbidity                     |                 |
| Diabetes mellitus               | 17 (38.6%)     |
| Hypertension                    | 34 (77.3%)     |
| Hypercholesterolemia or hypertriglyceridemia | 15 (34.1%)    |
| Severe renal dysfunction (cGFR < 60 mL/min/1.73 m²) | 14 (31.8%)    |

Tacrolimus doses and levels after conversion
Mean dose of tacrolimus was 2.65 ± 1.24 mg/day before conversion and 2.09 ± 1.68 mg/day after conversion (\( P < .05 \)), with ratio of 1:0.79. Mean serum tacrolimus trough level increased after conversion (preconversion level of 4.92 ± 1.65 ng/mL vs postconversion level at 1 mo of 5.60 ± 2.89 ng/mL; \( P < .05 \)), with ratio of 1:1.14. Three months after conversion, mean dose of tacrolimus was 1.69 ± 1.01 mg/day and mean serum tacrolimus trough level was 4.82 ± 1.91 ng/mL, similar to initial levels before conversion (\( P = .68 \)) (Figure 1). At 6 months after conversion, mean dose of tacrolimus was 1.65 ± 0.93 mg/day and mean serum tacrolimus trough level was 4.82 ± 1.85 ng/mL, similar to initial levels before conversion (\( P = .71 \)) (Figure 1). Finally, the dose ratio for similar tacrolimus exposition was 1:0.62.
Immunosuppressive regimen after conversion
At the end of the 6-month follow-up, 1 patient died (from suicide), 41 patients were still on ER-Tac, and 2 patients had returned to PR-Tac because of adverse effects (allergy, digestive trouble), which resolved thereafter.

Liver graft function after conversion
Aspartate and alanine transaminase and gamma-glutamyl transpeptidase levels remained stable between conversion and end of follow-up (29 ± 30, 31 ± 30, and 107 ± 191 IU/L vs 30 ± 30 [P = .87], 26 ± 17 [P = .55], and 112 ± 287 [P = .72] IU/L, respectively).

Renal function and rejection after conversion
Initial estimated glomerular filtration rate was 62.60 ± 21.51 mL/min versus 62.25 ± 22.00 mL/min 6 months after conversion (P = .67). No biopsy-proven acute rejection was observed during the follow-up period of 6 months after conversion.

Arterial hypertension, diabetes mellitus, and dyslipidemia after conversion
At the end of the follow-up, no differences (P > .99) were observed in the prevalence of arterial hypertension (34 patients, 77.3%). The prevalence of diabetes mellitus and dyslipidemia also remained unchanged (both P > .99) after conversion (17 patients/38.6% for diabetes mellitus and 15 patients/34.1% for dyslipidemia).

Cost
The mean cost of tacrolimus therapy was 5.54 ± 2.29 Euros/patient/day before conversion and 4.11 ± 2.32 Euros/patient/day (ratio of 1:0.74) 6 months after conversion (P < .05).

Discussion
As reported in the United States, tacrolimus is the most common drug used in transplant recipients. Initially, tacrolimus was developed as an immediate release formulation, requiring twice-daily dosing. Because lifelong immunosuppression is necessary to maintain allograft function in transplant recipients, nonadherence has been associated with graft failure. The first prolonged-release formulation of tacrolimus (Advagraf) was developed with the aim of improving adherence to treatment by reducing the dosage schedule of tacrolimus to once daily instead of twice daily. Comparative studies on Prograf (Astellas Pharma Europe Limited, Middlesex, UK) and Advagraf in LT recipients demonstrated similar efficacy and similar tolerability profiles, although systemic tacrolimus exposure was reduced with the once-daily formulation. Interestingly, improved adherence in renal transplant recipients was reported using this once-daily formulation. In a French observational study of LT and kidney transplant recipients, adherence was significantly dependant on sex, age at transplant, need for retransplant, and time elapsed since transplant, with rate of good adherence significantly higher in patients taking lower numbers of immunosuppressive drugs (45% for 1 vs 24% for 3 drugs). The transplant unit of Padua reported 68 LT patients who were switched from twice-daily to once-daily tacrolimus. The rate of patients who reported being late in taking their immunosuppressive drugs dramatically decreased after conversion (50% vs 6.3%) and so did the percentage of patients who reported forgetting to take their immunosuppressive medications at least once per month (46.9% vs 15.6%). These results are encouraging and need to be confirmed in a larger series. In addition, a recent large retrospective analysis of the European Liver Transplant Registry identified significant improvements in long-term graft and patient survival rates in patients treated with once-daily tacrolimus compared with regular twice-daily tacrolimus in primary LT recipients over 5 years of treatment.

A second tacrolimus prolonged release formulation (Envarsus) utilizes a drug delivery technology designed to enhance the bioavailability of drugs with
low-water solubility by creating a “solid solution” of the drug, the so-called MeltDose technology (Chiesi SAS, Nanterre, France). The drug delivery technology used breaks the drug particles down into small units, which are sprayed onto a carrier, forming a granulate, that is then compressed into tablets with a stable dissolution profile and particle size. This smaller drug particle size is associated with a greater drug surface area and thus a greater drug absorption. In comparison, Advagraf is formulated with a protective polymer coating of ethylcellulose, hypromellose, and lactose monohydrate around the drug, resulting in a slow release of the drug. Pharmacokinetics of Envarsus has been compared with tacrolimus immediate release, and adult kidney transplant and LT recipients required a 30% lower daily dose of Envarsus than tacrolimus immediate release to achieve similar systemic exposure levels at 1 week, as shown in phase 2 conversion studies. Presently, only scarce clinical data are available in LT recipients, which have mainly focused on pharmacokinetic data. Alloway and colleagues, in a phase 2 study, studied the conversion from Prograf to Envarsus in adult stable LT patients. The mean conversion ratio was 0.71, and pharmacokinetics data demonstrated consistent exposure at this conversion dose. Maximum concentration, maximum-to-minimum concentration ratio, percent fluctuation, and swing were significantly lower and time of maximum concentration was significantly longer for Envarsus. To date, there have been few direct pharmacokinetic comparisons of the 2 once-daily formulations of tacrolimus (Advagraf and Envarsus) in solid-organ transplant recipients. Recently, Tremblay and colleagues compared all 3 formulations of tacrolimus (IR-Tac, PR-Tac, and ER-Tac) in 30 stable renal transplant recipients. Patients were dosed with each drug for 7 days, and blood samples were obtained over 24 hours. A conversion factor of 1:1:0.80 for IR-Tac:PR-Tac:ER-Tac was used; no dose adjustments were permitted during the study. The observed exposure of IR-Tac was used to normalize exposure for PR-Tac and ER-Tac, resulting in the following recommended total daily dose conversion rates: IR-Tac:PR-Tac, +8%; IR-Tac:ER-Tac, -30%; and PR-Tac:ER-Tac, -36%. In the present study, we confirmed that a quite similar reduction dose (38%) is needed in cases of conversion from PR-Tac to ER-Tac in adult stable LT patients. We experienced some delay for obtaining the right conversion dose ratio because of the few available formulations of ER-Tac (0.75, 1, and 4 mg); therefore, it was difficult to use in patients who received low doses of tacrolimus. Finally, the conversion led to a significant reduced cost of tacrolimus therapy in our study (26%). Nevertheless, it must be pointed out that initial close drug monitoring to adapt the dose of ER-Tac after conversion induced additional costs. In our experience, a new steady state was obtained rapidly, less than 3 months after conversion.

Despite a short follow-up, we found no reported concerns regarding adverse events after conversion (only 2 patients presented minimal adverse events [allergy and digestive trouble], probably related to excipient or changes in pharmacokinetics of the drugs). We observed no cases of biopsy-proven acute rejection in our 44 patients. Nevertheless, it can be hypothesized that this may have been underestimated in the absence of protocol liver biopsies. We did not find a significantly increased risk of arterial hypertension, hypercholesterolemia, or diabetes mellitus in our cohort. Liver function tests remained unchanged in our patients, and we did not observe significant renal function variation.

Because available data strongly support that once-daily tacrolimus is therapeutically equivalent to the twice-daily formulation, with similar adverse effects, the question remains of its potential benefits in daily practice. As discussed above, improved adherence was strongly suggested. In addition, reduced frequency of dosing may have also benefitted the health-related quality of life in our patients. Finally, the 2 formulations of once-daily tacrolimus are different (tablets or capsules), and this could also affect patients’ preferences. Some observational studies evaluating this point are ongoing.

In conclusion, our results, from the first available cohort of solid-organ transplant recipients, indicate that conversion from once-daily PR-Tac (Advagraf) to once-daily ER-Tac (Envarsus) in stable LT patients is safe and cost-effective; however, initial dose adaptations and careful monitoring are still required.

References


