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Safety and Efficacy of Once-Daily Modified-Release Tacrolimus in Liver Transplant Recipients: A Multicenter Postmarketing Surveillance in Japan

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ABSTRACT

Introduction. Modified-release formulation of tacrolimus (TAC-MR) has been developed with the intent of improving patient adherence and quality of life. A number of studies have indicated that the efficacy and safety of once-daily TAC-MR were comparable with those of the original formulation, twice-daily tacrolimus. However, its dosage, trough level, safety, and efficacy in the multicenter clinical experience of Japanese liver transplant recipients have not been reported.

Methods. This postmarketing surveillance designed as an open-label, prospective, noninterventional observational study was performed. The 24 patients were enrolled for de novo transplantation, and the 122 patients were enrolled for conversion to TAC-MR from 22 medical institutions in Japan. The observation period is 1 year in de novo transplantation, and 24 weeks in conversion.

Results. Regarding de novo transplant, the median daily TAC-MR dose was 0.041 mg/kg/d at 1 day after transplantation, and the median tacrolimus trough level was 5.5 ng/mL at 3 days after transplantation. The most common adverse drug reactions were infections, at an incidence rate of 25.0%. The most common infections were cytomegalovirus viremia, at an incidence rate of 12.5%. Both patient and graft survival rates at 1 year were 94.1% and the rejection rate was 20.8%. Regarding conversion to TAC-MR, the median daily conventional TAC dose before conversion was 1.8 mg/d, and the daily TAC-MR dose was 1.5 mg/d. The median TAC trough level was 3.6 ng/mL before conversion and 3.5 ng/mL 1 week after conversion. The most common adverse drug reactions were infections, at an incidence rate of 5.1%. Episodes of death or graft loss did not occur, and there were 3 episodes of rejection. After conversion to once-daily TAC-MR, the patients' adherence was improved.

Conclusion. This study shows that a TAC-MR–based immunosuppressive regimen is safe and effective as used in Japanese clinical practice.

THE EFFICACY and safety profiles of tacrolimus (TAC) as an immunosuppressive agent to prevent graft rejection are well defined [1,2]. A once-daily TAC modified-release formulation (TAC-MR) has been developed as a dosing alternative that enables the same patient care strategies and therapeutic monitoring techniques as used with the original formulation of TAC. Because nonadherence with dosing can be a significant factor resulting in graft rejection and late graft loss, a once-daily dosing regimen could be a beneficial addition to the existing treatment armamentarium [3–5]. A number of studies have

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indicated that the efficacy and safety of once-daily TAC-MR are comparable with those of the original formulation, twice-daily TAC in de novo transplant recipients [6–8], and some studies have indicated that stable liver transplant recipients can be safely switched from twice-daily TAC to once-daily TAC-MR [6,9–11]. However, the dosage and trough level of TAC-MR and the safety and efficacy in the multicenter clinical experience have not been reported. Herein, we report the results of a nationwide postmarketing surveillance (PMS) of TAC-MR in Japan.

METHODS

This PMS study was designed as an open-label, prospective, noncomparative, noninterventional observational study. Patients were enrolled from March 2009 to March 2011. Information regarding the patients' characteristics was collected. The safety, efficacy, and adherence were evaluated, and the dosage of TAC-MR and the TAC trough level also were monitored. The observation period of de novo transplant was 1 year, and that of conversion was 24 weeks.

This study was conducted in accordance with a protocol approved by the Ministry of Health, Labour and Welfare (MHLW). A written agreement was obtained from participating institutions. The study was also in accordance with the standards for Good Post-Marketing Study Practice (GPSP) provided by the MHLW in Japan. The MHLW instructed the investigators to perform the PMS study according to GPSP, which is the authorized standard for PMS studies of approved drugs in clinical practice; therefore, no formal ethics committee approval was necessary. The PMS study in Japan is allowed to be conducted without informed consents. This study was carried out in clinical practice settings in Japan.

Terminology of the Medical Dictionary for Regulatory Activities/Japanese edition (MedDRA/J) version 11.1 was mainly used for summarizing and reporting adverse drug reactions (ADRs). Particular attention was paid to monitoring the occurrence of infections, glucose tolerance, renal impairment, impaired cardiac function disturbances, pancreatic dysfunction, neuropsychiatric disorders, and lymphoma or malignancy, which are identified safety concerns. ADRs were recorded with the physician's assessment of causality, and seriousness according to the International Conference on Harmonization standards. The efficacy was evaluated using the cumulative incidence rates of acute rejection, patient survival, and graft survival. Those cumulative incidence rates were calculated using Kaplan-Meier analysis.

RESULTS

De Novo Transplantation

Twenty-four patients were enrolled from 5 medical institutions in Japan. The patient characteristics are shown in Table 1. Both of the safety and efficacy analysis sets included 24 patients, who received organ donation from 23 living donors and 1 brain-dead donor. For 5 patients (20.8%), immunosuppression was started with TAC-MR before the scheduled transplantations, and the mean (standard deviation [SD]) duration of pretransplantation administration was 1.4 (0.55) days. For 12 patients (50.0%), immunosuppression was started with TAC intravenous administration, and the mean (SD) duration of post-transplantation intravenous administration was 9.9 (2.97) days.

Table 1. Patient Characteristics (De Novo)

Patient Characteristics	
Total	24
Gender (male/female)	12/12
Age (y)	
<15	0 (0.0)
≥15 <30	4 (16.7)
≥30 <40	1 (4.2)
≥40 <50	4 (16.7)
≥50 <65	13 (54.2)
≥65	2 (8.3)
Mean ± SD	50.3 ± 14.26
Body weight (kg)	57.7 ± 9.51
Donor (brain death/living)	1/23
MELD score	
<20	15 (62.5)
≥20	6 (25.0)
Child-Pugh classification	
A	3 (12.5)
B	8 (33.3)
C	12 (50.0)
ABO incompatible	1 (4.2)
Immunosuppression regimen	
TAC-MR monotherapy	1 (4.2)
Prednisolone	22 (91.7)
Mycophenolate mofetil	11 (45.8)

The median (Q1–Q3) TAC-MR dose was 0.041 mg/kg/d (range, 0.036–0.051) at 1 day after transplantation, and 0.058 mg/kg/d (range, 0.025–0.077) at 24 weeks after transplantation. The median (Q1–Q3) TAC trough level was 5.5 ng/mL (range, 2.80–10.30) at 3 days after transplantation, 10.6 ng/mL (range, 6.70–13.20) at 4 weeks after transplantation, and 5.2 ng/mL (range, 4.40–7.80) at 24 weeks after transplantation (Fig 1). The patients' adherence rate was 90% or higher in all patients.

The most common ADRs were infections at an incidence rate of 25.0%. The most common infections were cytomegalovirus viremia, at an incidence rate of 12.5% (Table 2).

The cumulative incidence rates of patient and graft survival at 1 year were 94.1%. The cumulative acute rejection rate was 20.8% and the steroid-resistant rejection rate was 4.2 % (Table 3).

Conversion to TAC-MR

One hundred twenty-two patients were enrolled from 22 institutions in Japan. The patient characteristics are shown in Table 4. Both of the safety and efficacy analysis sets included 117 patients. The mean (SD) duration after the transplantation until conversion to TAC-MR was 5.2 (4.39) years.

The median (Q1–Q3) twice-daily conventional TAC dose before conversion was 1.8 mg/d (range, 1.00–3.00), and the once-daily TAC-MR dose at the converted day was 1.5 mg/d