Once-daily, prolonged-release tacrolimus versus twice-daily, immediate-release tacrolimus in de novo living-donor liver transplantation: a Phase 4, randomized, open-label, comparative, single-center study

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Randomized, open-label, comparative, single-center, Phase 4, 24-week study comparing pharmacokinetics (PK), safety, and efficacy of once-daily, prolonged-release tacrolimus (PR-T) with twice-daily, immediate-release tacrolimus (IR-T) in adult de novo living-donor liver transplant (LDLT) recipients in Korea. All patients received intravenous tacrolimus from Day 0 (transplantation) for 4 days and were randomized (1:1) to receive oral PR-T or IR-T from Day 5. PK profiles taken on Days 6 and 21 (Fig1). Primary endpoint: area-under-the-concentration–time curve over 24h (AUC0–24). Predefined similarity interval for confidence intervals of ratios: 80–125%. Secondary endpoints included: tacrolimus concentration at 24h (C24), patient/graft survival, biopsy-confirmed acute rejection (BCAR), treatment-emergent adverse events (TEAEs). One-hundred patients were included (PR-T, n=50; IR-T, n=50). Compared with IR-T, 40% and 66% higher mean PR-T daily doses resulted in similar AUC0–24 between formulations on Day 6 (PR-T:IR-T ratio of means 96.8%, Fig2), and numerically higher AUC0–24 with PR-T on Day 21 (128.8%, Fig3), respectively. Linear relationship was similar between AUC0–24 and C24, and formulations. No graft loss/deaths; incidence of BCAR and TEAEs similar between formulations. Higher PR-T versus IR-T doses were required to achieve comparable systemic exposure in Korean de novo LDLT recipients. PR-T was efficacious; no new safety signals were detected.

Fig1

Transplantation (Day 0) Pharmacokinetic profile 1 Pharmacokinetic profile 2

IV tacrolimus Oral prolonged-release tacrolimus or immediate-release tacrolimus

Time Day 1 Day 0 Week 2 Week 3 Week 4 Week 12 Week 24

Enrollment Visit schedule Study end

Prolonged-release tacrolimus or immediate-release tacrolimus (morning dose)
Prolonged-release tacrolimus Hour 0 1 2 3 4 6 8 12 16 24

Immediate-release tacrolimus Hour 0 1 2 4 6 8 12 13 16 24

Profile taken on Day 6 and Day 21 Pharmacokinetic sampling time point

Fig2

Day 6, normalized data
- Prolonged-release tacrolimus
- Immediate-release tacrolimus

Fig3

Day 21, normalized data
- Prolonged-release tacrolimus
- Immediate-release tacrolimus