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Original Investigation

Novel Once-Daily Extended-Release Tacrolimus Versus Twice-Daily Tacrolimus in De Novo Kidney Transplant Recipients: Two-Year Results of Phase 3, Double-Blind, Randomized Trial

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Background: 1-year data from this trial showed the noninferiority of a novel once-daily extended-release tacrolimus (LCPT; Envarsus XR) to immediate-release tacrolimus (IR-Tac) twice daily after kidney transplantation.

Study Design: Final 24-month analysis of a 2-armed, parallel-group, randomized, double-blind, double-dummy, multicenter, phase 3 trial.

Setting & Participants: 543 de novo kidney recipients randomly assigned to LCPT (n = 268) or IR-Tac (n = 275); 507 (93.4%) completed the 24-month study.

Intervention: LCPT tablets once daily at 0.17 mg/kg/d or IR-Tac twice daily at 0.1 mg/kg/d; subsequent doses were adjusted to maintain target trough ranges (first 30 days, 6-11 ng/mL; thereafter, 4-11 ng/mL). The intervention was 24 months; the study was double blinded for the entirety.

Outcomes & Measurements: Treatment failure (death, transplant failure, biopsy-proven acute rejection, or loss to follow up) within 24 months. Safety end points included adverse events, serious adverse events, new-onset diabetes, kidney function, opportunistic infections, and malignancies. Pharmacokinetic measures included total daily dose (TDD) of study drugs and tacrolimus trough levels.

Results: 24-month treatment failure was LCPT, 23.1%; IR-Tac, 27.3% (treatment difference, −4.14% [95% CI, −11.38% to +3.17%], well below the +10% noninferiority criterion defined for the primary 12-month end point). Subgroup analyses showed fewer treatment failures for LCPT versus IR-Tac among black, older, and female recipients. Safety was similar between groups. From month 1, TDD was lower for LCPT; the difference increased over time. At month 24, mean TDD for LCPT was 24% lower than for the IR-Tac group ($P < 0.001$), but troughs were similar (means at 24 months: LCPT, 5.47 ± 0.17 ng/mL; IR-Tac, 5.8 ± 0.30 ng/mL; $P = 0.4$).

Limitations: Trial participant eligibility criteria may limit the generalizability of results to the global population of de novo kidney transplant recipients.

Conclusions: Results suggest that once-daily LCPT in de novo kidney transplantation has comparable efficacy and safety profile to that of IR-Tac. Lower TDD reflects LCPT's improved bioavailability and absorption.

INDEX WORDS: Immunosuppression; tacrolimus; kidney transplantation; extended-release; formulation; bioavailability; efficacy; treatment failure; safety; biopsy-proven acute rejection; Envarsus; pill burden; transplant recipient; end-stage renal disease (ESRD); randomized controlled trial (RCT).

Tacrolimus is overwhelmingly used as an immunosuppressant in kidney transplantation, both early posttransplantation and as part of long-term maintenance regimens.[1] While highly effective in preventing acute transplant rejection, tacrolimus has several limitations, including a narrow therapeutic window (necessitating drug monitoring and individual dose titration[2]), interindividual variation in absorption, and low bioavailability (17% ± 10%) of the currently widely used immediate-release tacrolimus

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(IR-Tac) twice-daily capsule formulation (Prograf; Astellas Pharma US, Inc).[3] In addition, both the IR-Tac formulation and another extended-release once-daily tacrolimus formulation (Advagraf/Astagraf XL; Astellas Pharma US, Inc) are associated with similar peak concentrations[4]; unwanted tacrolimus-associated neurologic adverse events (AEs) have been noted to happen or be most pronounced at peak serum tacrolimus blood concentrations.[5-7] Additionally, the twice-daily formulation adds further pill burden to a patient population already encumbered with taking many long-term medications. Multiple daily drug dosing is associated with increased risk for nonadherence[8-10]; this may result in acute rejection[11] and, in severe cases, transplant failure.[12]

The medication LCP-Tacro (LCPT; Envarsus XR; Veloxis Pharmaceuticals) is an extended-release tablet formulation of tacrolimus with once-daily dosing that has been developed using a proprietary MeltDose drug delivery technology (Veloxis Pharmaceuticals), distinguishing LCPT from other once-daily extended-release tacrolimus products (eg, Astagraf XL). The MeltDose technology decreases a drug's particle size to the smallest possible units as single molecules (ie, a "solid solution").[13] Drug particle size critically affects drug dissolution and absorption; if particle size is smaller, the surface area of the drug increases and the drug will be dissolved more quickly, resulting in better absorption.[14] Results of the MeltDose technology are increased absorption and bioavailability associated with LCPT tablets compared with other extended-release and IR tacrolimus formulations currently available. Phase 1 and phase 2 trials confirmed that LCPT enables broader absorption throughout the gastrointestinal tract and sustains consistent tacrolimus concentrations.[15] In addition, LCPT showed a lack of diurnal variability[16] common with other formulations.[3,17]

Phase 2 trials of de novo and stable kidney[18,19] and liver recipients[20,21] showed a steadier and more consistent concentration-time profile over 24 hours, with reduced peak and peak-to-trough fluctuations for LCPT compared to IR-Tac, increased bioavailability of ~30%, and comparable efficacy and safety profiles. A robust correlation between the area under the curve at 24 hours and the minimum concentration was also shown, indicating that therapeutic drug monitoring of minimum concentration as a measure of tacrolimus exposure can be applied to LCPT. A phase 3 conversion trial showed that LCPT had noninferior efficacy and comparable safety profile to IR-Tac, with lower doses (~20% lower than IR-Tac overall and 30% lower in white patients) of LCPT.[22]

Previously, the 12-month primary efficacy and safety outcomes were reported from this phase 3 double-blind double-dummy trial of de novo kidney transplant recipients randomly assigned to LCPT or IR-Tac.[23] Here, the prespecified blinded efficacy and safety outcomes at 24 months' follow-up are reported from this same phase 3 trial. Efficacy was also analyzed within patient subgroups (ie, females, blacks, and recipients aged ≥ 65 years) in order to explore the consistency of results, or lack thereof, within specific patient populations.

METHODS

Study Overview

This was a 2-armed, parallel group, prospective, randomized, double-blind, double-dummy, multicenter, 24-month, phase 3 trial. The study design has been previously reported.[23] Both the 1- and the 2-year analyses were a priori planned as explicitly stated in the study protocol. The primary endpoint was based on the 1-year analysis and the 2-year analysis was the final analysis designed to assess long-term efficacy and safety outcomes; patients and investigators stayed blinded for the full 24 months. In brief, adult de novo recipients of a living or deceased donor kidney transplant were randomly assigned to receive LCPT tablets once daily on a starting dose of 0.17 mg/kg/d or IR-Tac twice-daily (Prograf) capsules at 0.1 mg/kg/d. Subsequent doses of each study drug were adjusted to maintain whole-blood trough concentrations within the target range of 6 to 11 ng/mL for the first 30 days, then 4 to 11 ng/mL for the rest of the study. All patients also received a matching double-dummy placebo to maintain the blind. All patients also received mycophenolate mofetil (1 g twice daily) or mycophenolic acid (720 mg twice daily), an interleukin 2 receptor antagonist, and corticosteroids per local practice.

Key study exclusion criteria were as follows: receipt of an organ transplant other than kidney; panel-reactive antibody > 30%; body mass index < 18 or >40 kg/m^2; receipt of sirolimus, everolimus, azathioprine, or cyclophosphamide within 3 months before enrollment; and abnormal laboratory values.

Health authority, ethics committee, and institutional review board approval were obtained at each participating center, and informed consent was obtained from all patients. The study was undertaken in accordance with the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Harmonized Tripartite Guidelines for Good Clinical Practice and conformed to the Declaration of Helsinki.

Study End Points

Efficacy

The incidence of treatment failures (any of the following: death, transplant failure, biopsy-proven acute rejection [BPAR; Banff grade ≥ 1A, using Banff 2007 criteria; based on centrally read biopsies], or loss to follow-up) within 24 months after randomization was compared between LCPT and IR-Tac for the overall sample and also stratified by the following subgroups: age (<65 and ≥65 years), race (black or nonblack), and sex (male or female).

The incidence of each individual event (death, transplant failure, BPAR, or loss to follow-up) within 24 months after the randomization date was also assessed. Efficacy results are reported for the overall 24-month study period and separately for the 0- to 12-month and 13- to 24-month periods.

Safety

Safety end points at 24 months included the following: incidence of AEs, serious AEs (SAEs), and discontinuations due to AEs; incidence of predefined potentially clinically significant laboratory values; new-onset diabetes after transplantation