Envarsus XR in African American Renal Transplant Recipients

NCT Number: NCT02956005

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Study Protocol

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Introduction

Tacrolimus is overwhelmingly used as an immunosuppressant in kidney transplantation, both early posttransplantation and as part of long-term maintenance regimens. While highly effective in preventing acute transplant rejection, tacrolimus has several limitations, including a narrow therapeutic window (necessitating drug monitoring and individual dose titration), interindividual variation in absorption, and low bioavailability of the currently widely used immediate-release tacrolimus (IR-Tac) twice-daily capsule formulation (Prograf; Astellas Pharma US, Inc).[1] 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[2]; unwanted tacrolimus-associated neurologic adverse events (AEs) have been noted to happen or be most pronounced at peak serum tacrolimus blood concentrations. 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; this may result in acute rejection and, in severe cases, transplant failure.

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. 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. 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[4]. In addition, LCPT showed a lack of diurnal variability common with other formulations.

Phase 2 trials of de novo and stable kidney and liver recipients 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[5].

Hypothesis

African American renal transplant recipients that receive Envarsus will have less tubular injury and calcenurin inhibitor toxicity compared with patients that receive tacrolimus IR.

Study Type/Design

This is a case control study where a prospective cohort will be started de novo on Envarsus at the time of renal transplantation.

Endpoints

Primary endpoint is to determine the rate of calcineurin inhibitor toxicity as measured by surveillance kidney biopsies.

Secondary endpoint is to determine the rate of development of donor specific antibodies of the patients treated with Envarsus vs the patients treated with immediate release tacrolimus.

Patient Recruitment

We will prospectively consent 100 African American patients that will be receiving kidney transplants at our center. This cohort will be matched with a retrospective cohort of African American renal transplant recipients who received renal transplant and were treated with immediate release tacrolimus.

Exclusion criteria will include patients that are not African American and patients that are younger than 18 years old.

Inclusion Criteria

1. African American race

2. Adult renal transplant recipients (≥18 y/o)
3. Previous adverse reaction or contraindication to the use of tacrolimus

Exclusion Criteria

1. Non African American race
2. Less than 18 y/o (pediatric patients)
3. Recipients of liver and small bowel transplants
4. Adverse reaction to tacrolimus

Statistical analysis:

Data will be analyzed using standard statistical methods using chi square test, students T-square test, kaplan-meyer curve. No statistical analysis has been performed to achieve adequate power as this an observational study.

Treatment Overview

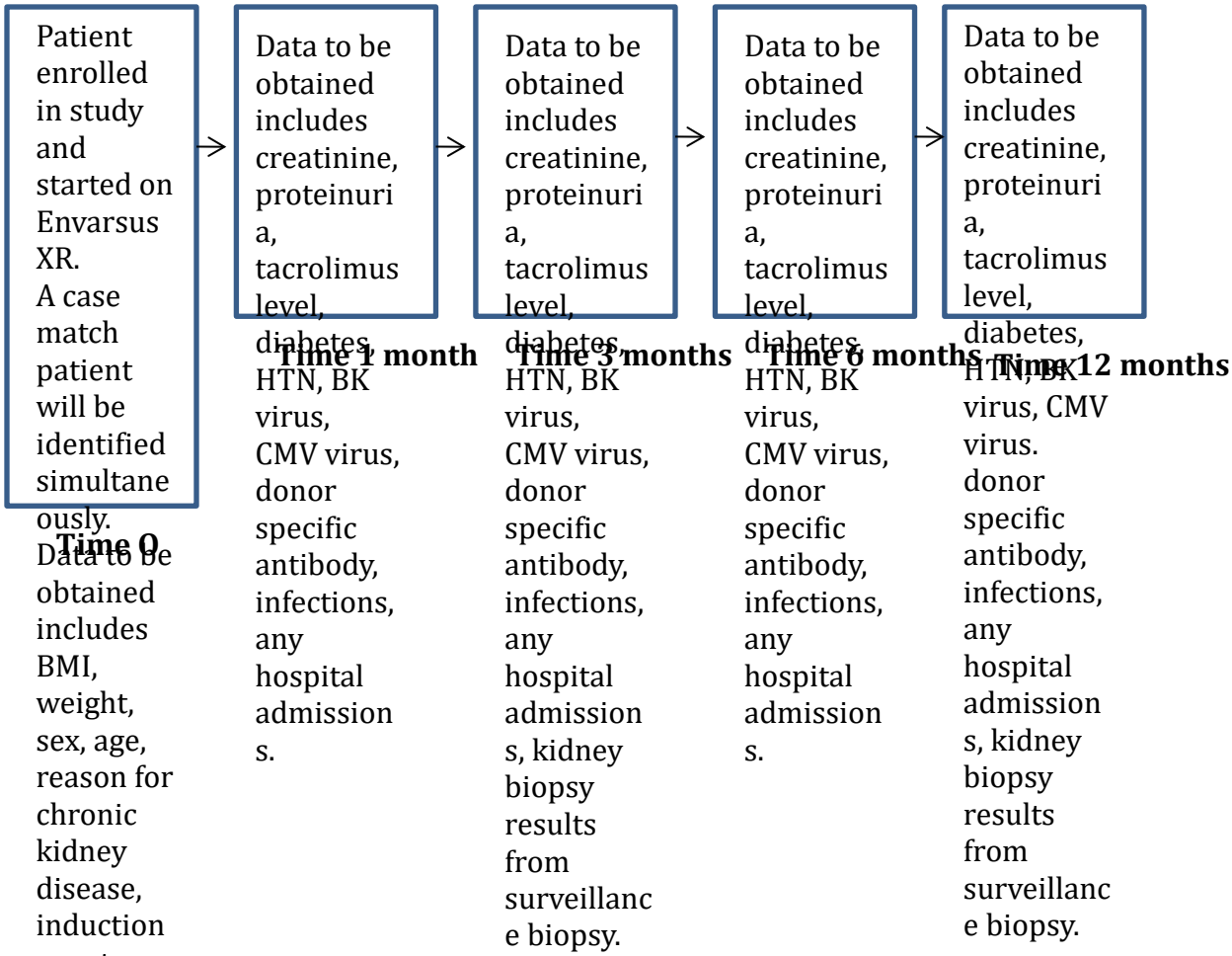
Screening will be performed by the Principal Investigators during the kidney transplant evaluation clinics, during the wait list kidney transplant evaluation clinic and prior to a schedule kidney transplant surgery.

Dosage and Administration of Envarsus XR

Patients enrolled in the prospective arm of the study will be started on Envarsus XR at 0.17mg/kg. The dose will be targeted to achieve a tacrolimus level between 8-10 ng/mL.

The tacrolimus level will be modified depending on the results of the surveillance biopsy, BK and CMV viruses, and donor specific antibody studies.

Laboratory Testing and Study Schedule
Schematic diagram of data that will be obtained during study:



Data to be obtained at time 0 on the prospective and retrospective cohort

1. BMI

2. Weight
3. Sex
4. Reason for chronic kidney disease
5. Induction agent
6. Crossmatch results
7. Type of donor
8. Donor age
9. Donor sex
10. Donor end creatinine
11. Donor's biopsy result if available

Data to be obtained at time 1 month, 3 month, 6 month and 12 month on the prospective and restrospective cohort

1. Creatinine level
2. Proteinuria
3. Tacrolimus level
4. Diabetes
5. Blood pressure
6. BK virus serum
7. CMV virus PCR
8. Donor specific antibody
9. Biopsy results (at 3 and 12 months surveillance and any other additional for cause biopsy that the patient may have had)

10. Infections
11. Hospital admissions
12. Blood transfusions (if any)

Patient Monitoring and Evaluation

Patients will have a kidney biopsy at time 0 (at the time of implantation and prior to reperfusion), 3 months and 12 months. If at any other time it is clinically necessary to perform another biopsy, it will be performed.

Potential Pitfalls and Contingencies

If a patient develops side effects that are attributed to tacrolimus, then the patient may have to be switched to another immunosupression regimen.

References

1. Prograf [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc; September 2013.
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3. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int. 2000;13(5):313-26.
4. Nigro V, Glicklich A, Weinberg J. Improved bioavailability of MELTDOSE once-daily formulation of tacrolimus (LCP-Tacro) with controlled agglomeration allows for consistent absorption over 24 hrs: a scintigraphic and pharmacokinetic evaluation. Presented at: American Transplant Congress; May 18-22, 2013; Seattle, WA. Abstract B1034.
5. Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT Trial. Am J Transplant 13 (3) (2013), pp.760-769.