. 2017 Feb;17(2):432-442

Efficacy and Safety of Once-daily Tacrolimus (Envarsus XR®) Conversion Therapy in Heart Transplantation

Miae Kim, PharmD, MS; Michael M. Givertz, MD; Garrick C. Stewart, MD; Deborah S. Page, APRN-BC; Erica L. Woodcome, ANP-BC; Mandeep R. Mehra, MD
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Background

- Tacrolimus-based immunosuppression can be limited by neurologic adverse reactions and consequent difficulty in titration of drug doses to therapeutic targets.
- Once-daily tacrolimus (LCP-tacrolimus [LCPT], Envarsus XR®) offers improved bioavailability and lower peak blood concentrations, which may lead to fewer neurological adverse effects while allowing for adequate therapeutic trough level titration.
- Little is known about the usefulness of LCPT in heart transplantation.

Purpose and Methods

- We aimed to evaluate outcomes in patients who were transitioned from immediate-release (IR) tacrolimus to LCPT.
- In this retrospective, single center analysis (1/2015-7/2019), 84 patients underwent heart transplantation, of whom 17 were converted to LCPT. The reasons for conversion included:
  - neurological adverse events (n=9), failure to achieve a therapeutic drug level with IR tacrolimus (n=4), or both (n=4).
- Outcomes of interest included symptom burden (neurotoxicity), frequency of rejection, and renal function (serum creatinine).

Results

- IR tacrolimus was converted to LCPT early post-transplant (median 1 month; range 0.5-11 months).
- Median equivalent dose conversion ratio was 0.77 (LCPT/IR Tacrolimus). Median dose-normalized concentration was significantly higher with LCPT vs. IR tacrolimus (0.65 ng/ml/mg vs 0.51 ng/ml/mg; p=0.01) (Figure 1).
- Dose stability trend was better with LCPT, which required 1.5 dose changes per month on average (range 0-6.7) as compared to 3.0 changes for IR tacrolimus (range 0-8.0; p=0.07).
- Among 13 patients transitioned for neurotoxicity, 8 (62%) reported improvement in symptoms, 4 (31%) no improvement, and 1 worsening of symptoms. In 7 (54%) patients, peak levels were checked (2-3 hours post dose) prior to conversion and were not elevated (median 18.1 ng/mL). (Table 1)

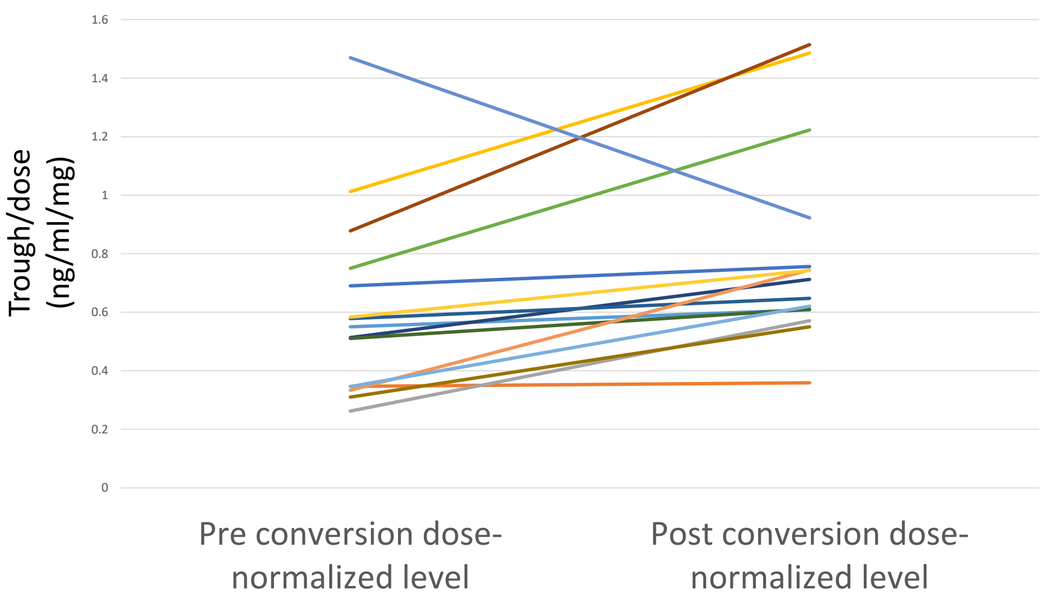

Figure 1. Dose normalized tacrolimus concentration before and after conversion

Two patients omitted due to interacting medication change.

Table 1. Changes in Neurotoxicity

Patient Number	Peak (ng/ml)	Neurotoxicity symptoms
1	17.5	Improved
2	19.1	Improved
3	35	Improved
4	16.7	Improved
5	33.4	Improved
6	15.5	Improved
7		Improved
8		Improved
9	28	No change
10		No change
11		No change
12		No change
13		Worsened

- ISHLT grade ≥ 2R rejections were infrequent and occurred in 1 patient on LCPT after intentional lowering of immunosuppression in the setting of invasive fungal infection.
- Renal function worsened 3 months after conversion to LCPT. Median serum creatinine prior to conversion was 0.99 mg/dL and 1.56 mg/dL after conversion (p=0.002) (Figure 2).

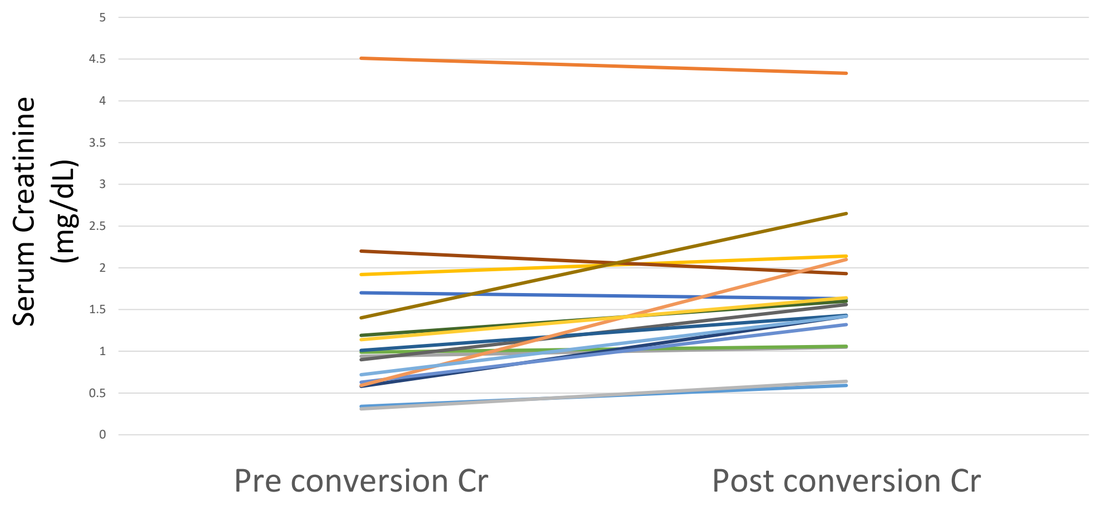

Figure 2. Serum Creatinine change (mg/dL) before and after conversion to LCPT

Limitations

- This study was not controlled against the no conversion group. Therefore, it is not clear if the findings in rejection and serum creatine seen in this study were related to LCPT conversion or other factors.
- This study evaluated only the short-term effect of LCPT conversion.

Conclusions

- LCPT conversion therapy in heart transplantation allows maintenance of therapeutic drug levels for those with difficulty achieving it with IR tacrolimus, and is associated with improved neurological symptoms and low rates of allograft rejection.
- Double-dummy randomized controlled trial is warranted to confirm these findings.

References

•Staatz CE, Tett SE. Clinical Pharmacokinetics of Once-Daily Tacrolimus in Solid-Organ Transplant Patients. *Clinical Pharmacokinetics*. 2015; 54:993-1025.

•Langone A, et al. Switching STudy of Kidney TRansplant PAtients with Tremor to LCP-TacrO (STRATO): an open-label, multicenter, prospective phase 3b study. *Clinical Transplantation* 2015;29(9):796-805

• Tremblay S, et al. A Steady-State Head-to-Head Pharmacokinetic Comparison of All FK-506 (Tacrolimus) Formulations (ASTCOFF): An Open-Label, Prospective, Randomized, Two-Arm, Three-Period Crossover Study. *Am J Transplant*. 2017 Feb;17(2):432-442

Conflict of Interest

No authors have direct or relevant financial disclosures to the matter presented. Dr. Mehra discloses the following general COIs: consultant for Abbott, Medtronic, Roivant, Janssen, Mesoblast, Bayer, Portola, Leviticus, FineHeart, NupulseCV, Baim institute for clinical research. He is also the Editor-in-Chief of the Journal of Heart and Lung Transplantation. We do discuss the use of off label medications.