Fluctuation Does Not Mean Variability: A Pharmacokinetic Point of View

F. Lemaître, C. Tron, M. Rayar

DR. MICHEL RAYAR (Orcid ID : 0000-0003-3113-2260)

Received Date : 02-Feb-2017

Revised Date : 08-Feb-2017

Accepted Date : 11-Feb-2017

Article type : L - Letter to the Editor

FLUCTUATION DOES NOT MEAN VARIABILITY: A PHARMACOKINETIC POINT-OF-VIEW

Florian Lemaitre[1,2,3], Camille Tron[1,2,3], Michel Rayar[2,3,4]

[1] Service de Pharmacologie Clinique et épidémiologique, Centre hospitalier Universitaire Pontchaillou, Rennes, France

[2] INSERM, CIC1414, Rennes, France

[3] Faculté de medecine, Université Rennes 1, Rennes, France

[4] Service de chirurgie hepatobiliaire et digestive, Centre hospitalier Universitaire Pontchaillou, Rennes, France

Corresponding author: Florian Lemaitre; florian.lemaitre@chu-rennes.fr

Dear editor,

We read with interest the article by Tremblay *et al.* (1) recently published in the American Journal of Transplantation and wanted to congratulate them for their study.

The authors reported a randomized, cross-over study comparing different formulations of tacrolimus (TAC) (immediate release (IR), extended release (ER) and the recently labelled once-daily tacrolimus formulation (LCPT)) in stable renal transplant recipients. Patients treated with IR-TAC were converted to ER-TAC with a dosage conversion factor of 1:1 on a mg basis or to LCPT with a dosage conversion factor of 1:0.8. As expected, the 1:0.8 conversion factor to LCPT resulted in higher TAC exposure. Indeed, in a phase II study, Osama Gaber *et al.* (2) have already explored the relationship between daily dose of TAC and exposure in 60 stable renal transplant recipients converted to LCPT and

concluded that, compared to IR-TAC dosage, a 30% dose reduction of LCPT produced similar areas under the curve (AUCs). Tremblay *et al.* strengthened this finding reinforcing the message for clinicians aiming at converting patients to LCPT.

The authors also found that LCPT is associated with less fluctuation between maximum ("peak") exposure and trough concentration with a lower peak exposure level than the other forms. However, this reduced fluctuation should not be misunderstood with a decrease of intrapatient nor interpatient variability. Indeed, fluctuation is defined as the ratio of the peak concentration (Cmax) minus trough concentration (Cmin) over the average concentration (Cav) (i.e. (Cmax – Cmin)/Cav) expressed as a percentage, while the variability (i.e the coefficient of variation (CV)), is defined by the ratio between the standard deviation of TAC Cmin over the mean value of measured TAC, in the same patient for intrapatient variability or between patients for interpatient variability (3).

As LCPT is a delayed absorption formulation with a progressive resorption throughout the digestive tract, its Cmax is lower that immediate release formulation, when normalized to the AUC, while Cmin is approximatively similar. Therefore, the value of Cmax-Cmin is lower with LCPT, while the Cav, which is dependent on AUC and time dosage interval (τ) (i.e. Cav = AUC/τ) is roughly similar between the different formulations when AUC is normalized. This implies that the fluctuation is necessarily lower with LCPT when compared to the IR-TAC or ER-TAC.

However, to date, the high fluctuation has no clinically relevance while high intrapatient variability could be a potential biomarker predictive of outcome (i.e. increase incidence of acute rejection, graft loss, apparition of *de novo* donor specific antibodies) (3-5). The interpatient variability (frequently expressed as the between-patient CV of AUCs) is also relevant as it describes the variability of drug exposure from one patient to another. Interestingly, in the study of Tremblay *et al.,* even if the population size is low, the CV of AUC tended to be higher for LCPT.

In conclusion, variability and fluctuation are two distinct parameters with a potential clinically relevance only for the first one. These terms should not be confused with one other and clinicians should be aware of this difference.

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the American Journal of Transplantation. FL received a research grant from Astellas SA. The other authors have no conflicts of interest to disclose.

References

1. Tremblay S, Nigro V, Weinberg J, Woodle ES, Alloway RR. 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; 17: 432–442.

2. Gaber AO, Alloway RR, Bodziak K, Kaplan B, Bunnapradist S. Conversion from twice-daily tacrolimus capsules to once-daily extended-release tacrolimus (LCPT): A phase 2 trial of stable renal transplant recipients. Transplantation 2013; 96: 191–197.
3. Borra LC, Roodnat JI, Kal JA, Mathot RA, Weimar W, van Gelder T. High within-patient variability in the clearance of tacrolimus is a risk factor for poor long-term outcome after kidney transplantation. Nephrol Dial Transplant 2010; 25: 2757–2763.
4. Rodrigo E, Segundo DS, Fernandez-Fresnedo G, et al. Within-patient variability in tacrolimus blood levels predicts kidney graft loss and donor-specific antibody development. Transplantation 2016; 100: 2479–2485.
5. Vanhove T, Vermeulen T, Annaert P, Lerut E, Kuypers DR. High intrapatient variability of tacrolimus concentrations predicts accelerated progression of chronic histologic lesions in renal recipients. Am J Transplant 2016; doi: 10.1111/ajt.