Fluctuation Does Not Mean Variability: A Pharmacokinetic Point of View

F. Lemaître, C. Tron, M. Rayar

To cite this version:

HAL Id: hal-01558820
https://hal-univ-rennes1.archives-ouvertes.fr/hal-01558820
Submitted on 12 Jul 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
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