Intrapatient variability in solid organ transplantation: Should we make the first move earlier?

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Intra-patient variability in solid organ transplantation: should we make the first move earlier?

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Dear editor,

We read with great interest the article of Gueta and colleagues and we wanted to congratulate the authors for this first observation of intra-patient variability (IPV) impact on clinical outcomes in heart transplant (HTx) recipients (1). Indeed, in their retrospective study conducted in 72 HTx patients, the authors found that the coefficient of variation (CV) of tacrolimus (TAC) whole-blood trough concentrations measured between 3 and 12 months is associated with worst mid- to long-term (total rejection score after the first year post-transplantation that is the sum of all biopsies grades

divided by the number of biopsies; 0.33 vs. 0, p=0.035) outcome. Despite this relatively small cohort, Gueta *et al.* found that high TAC CV was a tremendous risk factor for the onset of rejection (OR=8.52 [1.63-44.53], p=0.011) but not for mortality (probably due to a lack of statistical power).

TAC IPV has been now increasingly recognized as a relevant "biomarker" of clinical outcomes in most of solid organs transplantations. Several demonstrations have been made in renal transplantation (2,3) as well as in liver transplantation (4,5). However, while most of the studies, conducted on that topic, only included data beyond 6th month after transplantation, Gueta *et al.* included data from month-3 which is, in our point of view, a very relevant element. Indeed, the authors wisely pointed that TAC steady state is reached since the third day after treatment initiation which means that impact of TAC CV could be studied way before the 6th month. After such a long period, we believe that TAC CV is rather an observance "biomarker" than a reflect of patient's own variability causes and thus therapeutic actions aiming at reducing IPV consequences may be less efficient. In liver transplanted patients, our group demonstrated that TAC IPV, calculated as early as day-8, had already a significant impact on clinical outcomes. A threshold of TAC CV > 40% was significantly associated with a higher rate of neurologic complications (p<0.001), cardiovascular complications (p<0.001) and acute renal failure requiring dialysis (p<0.001). Graft survival was also significantly worse in the high-CV group (HR=1.42 [1.04; 1.95], p=0.03) (5).

Early identification of patients at-risk of worse outcomes secondary to a high TAC CV may then allow implementing actions aiming at reducing more efficiently its clinical consequences.

In this context, we strongly encourage renal and heart transplantation teams to evaluate the impact of early IPV.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

References:

1. Gueta I, Markovits N, Yarden-Bilavsky H, Raichlin E, Freimark D, Lavee J, et al. High tacrolimus trough level variability is associated with rejections after heart transplantation. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2018 IN PRESS-THIS ISSUE

2. Vanhove T, Vermeulen T, Annaert P, Lerut E, Kuypers DRJ. High intrapatient variability of tacrolimus concentrations predicts accelerated progression of chronic histologic lesions in renal recipients. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2016 Mar 25;

3. Whalen HR, Glen JA, Harkins V, Stevens KK, Jardine AG, Geddes CC, et al. High Intrapatient Tacrolimus Variability Is Associated With Worse Outcomes in Renal Transplantation Using a Low-Dose Tacrolimus Immunosuppressive Regime. Transplantation. 2017 Feb;101(2):430–6.

4. Shemesh E, Bucuvalas JC, Anand R, Mazariegos GV, Alonso EM, Venick RS, et al. The Medication Level Variability Index (MLVI) Predicts Poor Liver Transplant Outcomes: A Prospective Multi-Site Study. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg. 2017 Mar 20;

5. Rayar M, Tron C, Jézéquel C, Beaurepaire JM, Petitcollin A, Houssel-Debry P, et al. High Intrapatient Variability of Tacrolimus Exposure in the Early Period After Liver Transplantation Is Associated With Poorer Outcomes. Transplantation. 2018 Mar;102(3):e108–14.