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LETTER TO THE EDITOR

iPTH is not a significant factor influencing the tacrolimus C/D ratio

We appreciate our colleagues' findings on the interesting association between CYP3A5 polymorphism, serum intact-PTH (iPTH) levels, and tacrolimus (TAC) trough.[1] CYP3A4 and CYPA5 are important determinants of TAC metabolism, which can be described simply by the concentration-to-dose (C/D) ratio.[2] In a rat model, secondary hyperparathyroidism (SHPT) decreased CYP3A activity, whereas SHPT therapy with cinacalcet restored it.[3] Consistent with this finding, but in contrast to Suzuki et al.,[4] a positive correlation between iPTH level and TAC concentration was found in the present study by Tanaka et al.[1] and also a study by Hirata et al.[5]

However, the two latter studies included only a few patients (Tanaka et al.: 48 patients[1]; Hirata et al.: 12 patient[5]). Especially for small study groups, data points with extreme values have high leverage in correlation analysis. Co-administration of CYP3A inhibitors or inducers in some patients further blurs the results. In addition, the use of logistic regression to identify significant factors associated with the TAC C/D ratio, as outlined by Tanaka et al.,[1] requires the partitioning of the C/D ratio into a binary dependent variable. Therefore, we analyzed the data of 393 adult patients (kidney transplantation between 2007 and 2015) from our transplantation centre who were treated with TAC b.i.d. and had iPTH levels at transplantation and 3 month after transplantation. The C/D ratio was determined 3 months after transplantation. We performed two linear regressions to test the correlation between the TAC C/D ratio and the iPTH levels.

The plot shows a large scatter of TAC C/D values for iPTH levels at transplantation and 3 months after transplantation. Both linear regression models have a slope of zero (Figure 1). For both regression models, the coefficients of determination are <0.01. This clearly demonstrates that the iPTH level in our cohort does not correlate with the TAC C/D ratio. Our findings strongly contrast with the findings of Tanaka et al., who examined a Japanese cohort, and already pointed out that their results cannot be generalized to other ethnicities. However, the major shortcoming of their analysis is that the C/D ratio was not determined at a standardized timepoint after transplantation because it can fluctuate significantly over time.[2] Based on the high number of patients in our study, we conclude from our data that iPTH is not a major driver of the TAC C/D ratio.

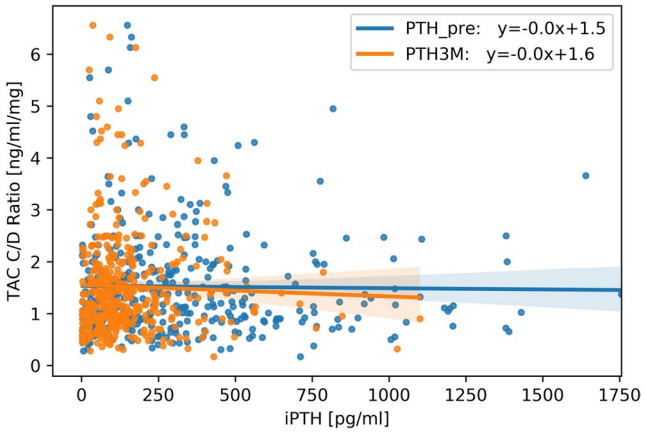

FIGURE 1 iPTH before transplantation: slope of −4.67e-05, standard error of 1.68e-04, *p* value of 0.78. iPTH 3 months after transplantation: slope of −2.23e-04, standard error of 3.52e-04, *p* value of 0.53. The highlighted areas display the 95% confidence intervals estimated by bootstrapping

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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