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LETTER TO THE EDITOR

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

We welcome Westphal et al.'s response to our recent publication. As they point out, our[1] and Hirata et al.[2] previous retrospective studies have very small sample sizes of 48 and 12 patients, respectively. In our paper, time points of measurements for tacrolimus (TAC) and intact parathyroid hormone (iPTH) were not standardized, and logistic regression analysis did not partition TAC concentration/dose (per body weight) ratio (C/D) into a binary dependent variable. Additionally, we did not investigate the influence of other uremic toxins, such as indoxyl sulfate, that accumulate in renal failure and may induce downregulation of cytochrome P450 (CYP) 3A protein expression.[3] Other factors, such as FGF23, ionized calcium, phosphorus, and vitamin D levels, that fluctuate in secondary hyperparathyroidism were also not evaluated. Therefore, as described in the limitation section of our report, we cannot rule out the possibility that iPTH correlates positively with other molecules that accumulate in renal failure and partially mediates elevation of TAC C/D.

Westphal et al. found that there was no correlation between iPTH and TAC C/D using a large number of 393 kidney transplant recipients. However, this letter does not seem to rule out the influence of concomitant drugs, such as CYP3A inhibitors and inducers. According to the report by Hirata et al.,[2] the positive correlation of iPTH level with TAC C/D was confirmed by excluding patients who received these concomitant drugs. In addition, our previous study found that the correlation coefficient of both factors increased from $r = 0.305$ to 0.428 by excluding these patients.[1] However, kidney transplant recipients take multiple medications for primary and comorbidities, some of which have CYP3A inhibitory activity. Thus, we also consider that iPTH levels may not correlate with TAC C/D in the entire patients who undergo kidney transplantation. Furthermore, as described in the limitation section of our report, there are racial differences in the prevalence of CYP3A5*1 carrier[4] and iPTH concentration.[5] Hence, our results cannot be generalized to other ethnicities.

Moreover, TAC is a typical substrate for P-glycoprotein. The bioavailability of TAC varies due to the difference in the expression level of P-glycoprotein.[6] Therefore, C/D alone cannot completely assess the metabolic activity of TAC. It is still controversial that iPTH may reduce the metabolic activity of TAC by decreasing the expression level of CYP3A. However, a large sample study by Béranger et al. suggests that iPTH is not a major driver of the TAC C/D ratio in kidney transplant recipients.

CONFLICT OF INTEREST

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