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LETTER TO THE EDITOR

Why dose adjust systemic exposure when looking for associations with adverse events in tacrolimus-treated transplant recipients?

The article by Campagne et al[1] highlights a timely issue in modern immunosuppressive therapy of transplanted patients; what is the impact of tacrolimus (Tac) exposure on extrarenal adverse effects? Unfortunately, the analyses done by Campagne et al cannot answer this question adequately. By dose adjusting the area under the curve (AUC) and maximum concentration (C_{max}) values, the authors calculate the inverse of clearance (CL) since AUC = Dose/CL, and hence AUC/Dose = 1/CL. In our opinion, the best way would have been to investigate the associations between the actual exposure of Tac in each individual (AUC, C_{max}, or C_0) and adverse effects. An earlier study has, for example, shown an association between reduced C_{max} and improvement of Tac-induced tremor.[2]

Relevant to the objective of the analysis performed by Campagne et al is that the dose of Tac in these patients have been individually adjusted to reach the same trough concentration target; ie, a patient with a low dose-adjusted AUC (ie, high CL) will need a higher dose to obtain the same trough concentration compared to a patient with a high dose-adjusted AUC (ie, low CL). Data presented in figure 2 are not according to what would be expected from earlier knowledge about tacrolimus side effects. In figure 2d, for example, a high dose-adjusted AUC is associated with high degree of neurological adverse effects. Following this logic, a patient showing a high dose-adjusted AUC, ie, low dose to reach target trough concentration and hence low C_{max}, will have a higher probability for occurrence of neurological adverse effects compared to a patient in need of a high dose (high C_{max}) to reach the same target. Is this correct interpretation of the presented data?

It is also not clear to us why the authors chose to present association analyses using both dose-adjusted AUC/C_{max} and the model estimated individual CL/F values to reveal potential associations with the extrarenal adverse effects. Both measures describe roughly the same pharmacokinetic properties as described above. It could of course be that a patient with high CL will get a high exposure of potentially toxic metabolites, but again, does not the presented data actually indicate the opposite?

In our opinion, this paper has revealed that each patient's Tac CL is associated with adverse event and one cannot easily change this pharmacokinetic parameter by changing the dosing schedule.

COMPETING INTERESTS

There are no competing interests to declare.

Keywords

adverse drug reactions, drug metabolism, other, pharmacokinetics, transplantation

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