LETTER TO THE EDITORS

Artificial intelligence improves estimation of tacrolimus area under the concentration over time curve in renal transplant recipients

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Dear Editors,

It has been shown that renal graft survival largely depends on the type and dosing of immunosuppressant treatments [1]. Tacrolimus, a widely-used calcineurin inhibitor, has a narrow therapeutic window, which makes regular drug monitoring necessary [2]. Interestingly, area under the concentration over time curve (AUC) correlates better with clinical complications, such as nephrotoxicity [3], infections, and acute rejection, compared to trough levels. However, AUC calculations are costly, as they may require up to eight sequential blood samples over 12 h [3]; blood samples over a 24 h period may be necessary for patients on extended release tacrolimus. For this reason, AUC calculations are also clinically impractical, especially in children and elderly patients. Here, we designed and implemented an artificial neural network to approximate immediate release tacrolimus AUC in renal transplant recipients. Neural network was a multi-layer perceptron network made of sigmoid neurons [4]; details about neural network are shown in Appendix S1. Neural network input was tacrolimus blood concentration at 3 h postdose (in ng/ml). Neural network output was neural network predicted AUC (nnAUC, in ng h/ml). 53 tuples consisting of tacrolimus blood concentration at 3 h postdose and its corresponding AUC measure were extracted from the literature (data are available in previous study [3]), and randomly split into a training batch (38 tuples) and a testing batch (15 tuples). The training batch was used to select the fittest neural network, using genetic algorithms [5]. The performance of the selected neural network was then evaluated on the testing batch. Patients' main characteristics can be found in previous reports [3]. There was no significant difference between mean AUC and mean nnAUC values (187 and 188.6 ng h/ml, respectively, $P = 0.95$). AUC and nnAUC variances were also not significantly different ($P = 0.60$). AUC and nnAUC distributions are shown in Appendix S1.

A Bland–Altman plot of AUC and nnAUC values is shown in Figure 1; bias was −1.5, and 95% limits of agreement ranged from −46.14 to 43.07. Correlation was 0.957.

In terms of accuracy, 93% of nnAUC values were within 30% of AUC; 87% of nnAUC values were within 10% of AUC.

In conclusion, artificial intelligence seems to be a fast, cheap, and clinically simple approach to estimate tacrolimus AUC in renal transplant recipients. Neural network only required tacrolimus blood concentration at 3 h postdose to compute nnAUC; this parameter, more precise than trough level [2], is cheap and easy to obtain, especially in children or elderly patients. Importantly, neural network predictions of tacrolimus exposure outperformed predictions of other models, including recent Bayesian models [2]. On another note, if the relevant characteristics of the target population vary, or if a change is made in the way an input is measured, a retraining of the neural network may be necessary to restore its prediction performance.

We hope that the better approximation of tacrolimus AUC obtained with artificial intelligence will allow

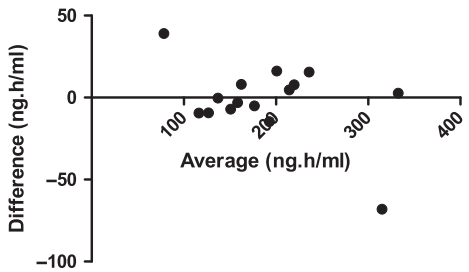

Figure 1 Bland–Altman plot of AUC and nnAUC; measures performed in the testing batch.

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clinicians to better monitor transplanted populations with an increased risk of inadequate tacrolimus dosing (particularly patients with poor adherence to treatments, suspected tacrolimus nephrotoxicity, or suspected rejection). Moreover, clinicians could decrease the frequency, and thus the cost and invasiveness of tacrolimus AUC measures during the follow-up of renal transplant recipients with an average to low risk of inadequate tacrolimus dosing.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Methods.

Figure S1. Architecture of the fittest neural network, including weights and biases.

Figure S2. Distribution of AUC and nnAUC; measures performed in the testing batch.

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