

Letter to the Editors

The *CYP3A4*22* allele affects the predictive value of a pharmacogenetic algorithm predicting tacrolimus predose concentrations

Laure Elens,^{1,4} Dennis A. Hesselink,² Ron H. N. van Schaik¹ & Teun van Gelder^{2,3}

Departments of ¹Clinical Chemistry, ²Internal Medicine and ³Hospital Pharmacy, Erasmus MC, Rotterdam, the Netherlands and ⁴Louvain Centre for Toxicology and Applied Pharmacology (LTAP), Université catholique de Louvain, Brussels, Belgium

The cytochrome P450 (CYP) 3A4*22 allelic status influences the pharmacokinetics of tacrolimus independently of an individual's *CYP3A5* genotype [1, 2]. In their recent publication, Passey *et al.* [3] described an algorithm that predicts tacrolimus apparent clearance (CL/F) by taking into account the age and *CYP3A5* genotype of a patient, time after kidney transplantation, whether the transplantation was performed at a steroid-sparing centre or not and whether the patient was treated with a calcium channel blocker (CCB) (Box 1). However, as the effect of the *CYP3A4*22* allele has only recently been reported, these authors did not consider this variable as a potential predictive factor for tacrolimus CL/F.

Box 1

Tacrolimus apparent clearance (CL/F) predictive equation [3]

$$\begin{aligned} \text{CL/F} = & 38.4 \times ([0.86, \text{if } 6-10 \text{ days}] \text{ or} \\ & [0.71, \text{if } 11-180 \text{ days}]) \\ & \times ([1.69, \text{if } \text{CYP3A5}^*1/^*3 \text{ genotype}] \text{ or} \\ & [2.00, \text{if } \text{CYP3A5}^*1/^*1 \text{ genotype}]) \\ & \times (0.70, \text{if receiving a transplant at a steroid} \\ & \text{- sparing centre}) \times \left(\left[\frac{\text{age in years}}{50} \right]^{0.4} \right) \\ & \times (0.94, \text{if CCB is present}) \end{aligned}$$

CL/F, apparent clearance; CCB, calcium channel blockers

The aim of the present report was to evaluate whether taking the *CYP3A4*22* allelic status into account affects the predictive value of the algorithm developed by Passey *et al.* [3]. The patients included in the present analysis were

185 *de novo* kidney transplant recipients treated with a tacrolimus-based regimen who participated in a trial comparing fixed-dose (FD) with concentration-controlled (CC) mycophenolate mofetil (MMF) treatment [4]. All patients had been previously genotyped for *CYP3A4*22* and *CYP3A5*3* alleles [1]. The required patient characteristics were inserted in the equation [3] to obtain the predicted tacrolimus CL/F for each individual. Predicted predose concentrations (C_{pred}) were then estimated according to the following equation:

$$C_{\text{pred}} (\text{ng ml}^{-1}) = \left(\frac{\text{dose administered} \times 1000}{\text{CL/F}} \right)$$

where CL/F is in l h^{-1} and the dose administered is the total daily dose of tacrolimus in mg divided by 24 h. In the FDCC study, information on the use of CCBs was not available. The corresponding term in the equation was thus left out of the algorithm but the resulting effect is assumed to be minor as (i) the concomitant use of a CCB is associated with only a small (6%) decrease in tacrolimus CL/F (Box 1) and (ii) an estimated 30–50% of the population are CCB users, and most are on dihydropyridine CCBs, which have only a limited effect on CYP3A activity [5]. As in the validation study of Passey *et al.* [6], the evaluation of the predictive performance of the equation was restricted to initial predose concentrations (days 3 and 10). The predictive values of the algorithm were estimated as described in this validation study [6]. The predictive performance for the estimation of predose concentrations was thus evaluated with individual prediction errors (PE_i). PE_i was calculated as the difference between C_{pred} and the corresponding observed predose concentration (C_{obs}):

$$PE_i = C_{\text{pred}} - C_{\text{obs}}$$

The bias was defined as the median prediction error (MPE = median PE_i) and the precision as the median absolute prediction error (MAPE = median PE_i). The significance of the inaccuracy of the prediction was assessed with one-sample Wilcoxon single rank test under the null hypothesis that the MPE or MAPE do not deviate from 0. To evaluate the difference in the performance parameters obtained in both *CYP3A4**22 carriers and *CYP3A4**1/*1 groups, we used a Mann-Whitney test under the null hypothesis that there is no difference in bias or precision between both *CYP3A4* genotype groups.

For the entire population, C_{obs} was plotted against C_{pred} (Figure 1A). We observed a bias (MPE) of +0.09 ng ml⁻¹ and a precision (MAPE) of 4.30 ng ml⁻¹. In their validation study, Passey *et al.* reported a bias of +0.2 ng ml⁻¹ [6], which is in line with our data. However, they reported a precision of 1.8 ng ml⁻¹ which reflects a lower relative scattering of their predicted values compared with ours. The MAPE in our study deviates significantly from 0 ($P < 0.001$). This lack of precision in our dataset could be due to the lower number of predose concentrations available in our study ($n = 265$) in comparison with the study of Passey *et al.* ($n = 412$) and/or the non-consideration of the use of CCBs. Nevertheless, a good accuracy of the equation was still observed and the slight C_{pred} overestimation (i.e. +0.09 ng ml⁻¹) is suggested to be minor as it was not significant ($P = 0.87$). When the analysis was performed by taking *CYP3A4**22 carriership into account (Figure 1B and C), in *CYP3A4**1/*1 homozygous patients the bias was +0.36 ng ml⁻¹ but not significantly different from 0 ($P = 0.70$). By contrast, in *CYP3A4**22 carriers, a negative bias of -5.24 ng ml⁻¹ was observed, which did significantly deviate from 0 ($P = 0.013$). The difference in bias observed in both groups was significant (0.36 vs. -5.24 ng ml⁻¹, $P = 0.011$).

As the *CYP3A4**22 allele has been previously associated with a reduced tacrolimus clearance [1, 2], it is not surprising that an algorithm that does not take into account the *CYP3A4**22 genotype will overrate the individual's ability to metabolize the drug. Indeed, predose concentrations are thus underestimated and, as a result, a negative bias is observed. This information is important as using this algorithm for *CYP3A4**22 carriers may lead to prescription of a too high tacrolimus dosage, which could predispose these patients to drug overexposure and increase their risk of adverse events. The difference in precision was not significant between *CYP3A4**22 genotype groups (4.2 ng ml⁻¹ vs. 5.3 ng ml⁻¹ for *CYP3A4**1/*1 and *CYP3A4**22 carriers, respectively, $P = 0.97$). In conclusion, this report confirms that the previously published algorithm predicting tacrolimus clearance is able to determine early predose concentrations in the general population but might be inaccurate for patients carrying the *CYP3A4**22 decrease-of-function allele. Consequently, we believe that the equation should be refined and include the *CYP3A4**22 allelic status of the patient.

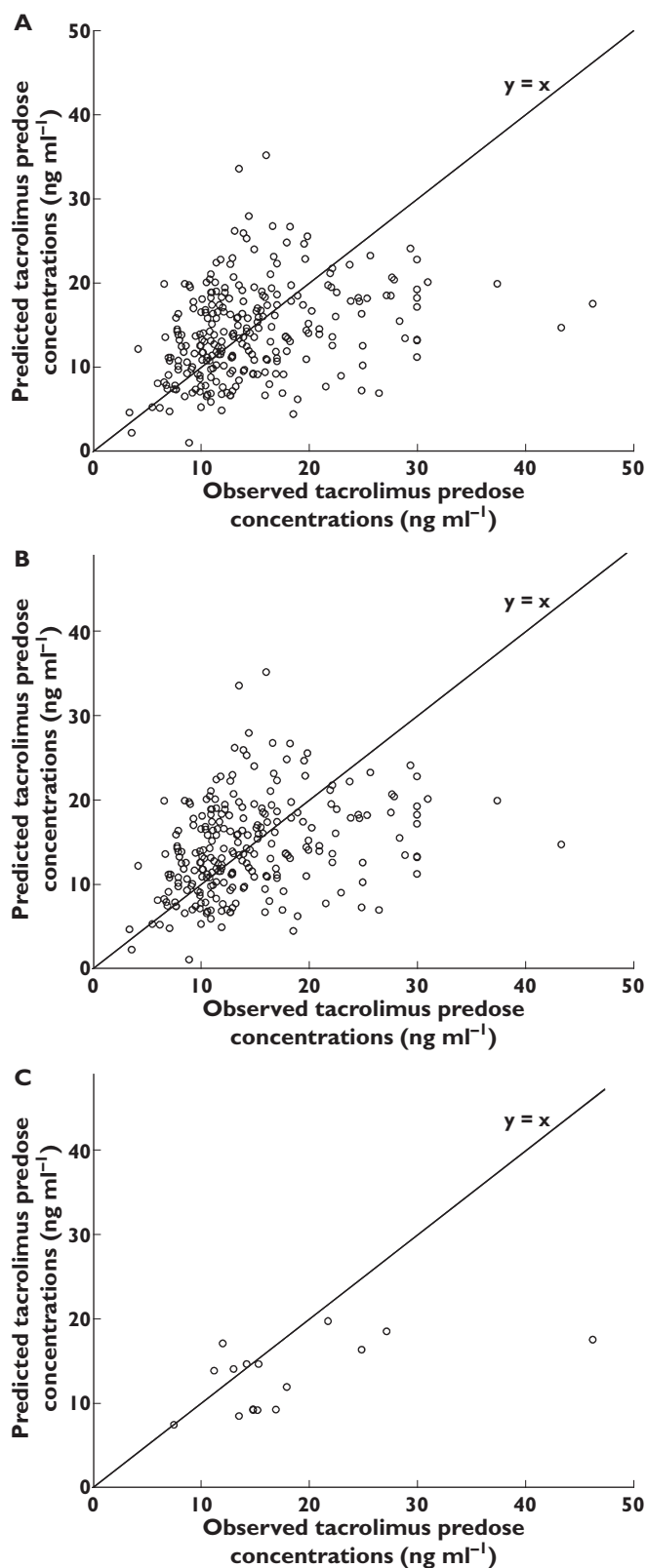


Figure 1 Observed tacrolimus predose concentrations vs. predicted tacrolimus predose concentrations in (A) the whole population, (B) *CYP3A4**1/*1 homozygous wild-type patients and (C) in *CYP3A4**22 carriers

Competing Interests

All authors have completed the Unified Competing Interest form and that they are available on request from the corresponding author. All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work

Editor's note

The authors (Passey *et al.*) of the cited BJCP article were offered the opportunity to comment on the letter but declined to do so.

Laure Elens is a post-doctoral researcher with the Fonds National de la Recherche Scientifique (FRS-FNRS), Belgium.

REFERENCES

- 1 Elens L, Bouamar R, Hesselink DA, Haufroid V, van der Heiden IP, van Gelder T, van Schaik RH. A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients. *Clin Chem* 2011; 57: 1574–83.
- 2 Elens L, van Schaik RH, Panin N, de Meyer M, Wallemacq P, Lison D, Mourad M, Haufroid V. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. *Pharmacogenomics* 2011; 12: 1383–96.
- 3 Passey C, Birnbaum AK, Brundage RC, Oetting WS, Israni AK, Jacobson PA. Dosing equation for tacrolimus using genetic variants and clinical factors. *Br J Clin Pharmacol* 2011; 72: 948–57.
- 4 van Gelder T, Silva HT, de Fijter JW, Budde K, Kuypers D, Tyden G, Lohmus A, Sommerer C, Hartmann A, Le Meur Y, Oellerich M, Holt DW, Tonshoff B, Keown P, Campbell S, Mamelok RD. Comparing mycophenolate mofetil regimens for *de novo* renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation* 2008; 86: 1043–51.
- 5 Ma B, Prueksaritanont T, Lin JH. Drug interactions with calcium channel blockers: possible involvement of metabolite-intermediate complexation with CYP3A. *Drug Metab Dispos* 2000; 28: 125–30.
- 6 Passey C, Birnbaum AK, Brundage RC, Schladt DP, Oetting WS, Leduc RE, Israni AK, Guan W, Matas AJ, Jacobson PA. Validation of tacrolimus equation to predict troughs using genetic and clinical factors. *Pharmacogenomics* 2012; 13: 1141–7.

RECEIVED

26 September 2012

ACCEPTED

14 October 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

16 November 2012

CORRESPONDENCE

Dr Laure Elens MSc, PhD, Louvain Centre for Toxicology and Applied Pharmacology (LTAP), Université catholique de Louvain, Avenue E. Mounier 53.02, 1200 Brussels, Belgium.
 Tel.: +32 2764 5354
 Fax: +32 2764 5338
 E-mail: laure.elens@uclouvain.be; l.elens@erasmusmc.nl