

## Response: Limited sampling strategies for once daily tacrolimus exposure monitoring

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Dear Sir,

We thank Dr. Antonio J. Carcas-Sansuán for his valuable comments. However, there is an important difference between the Madrid models and the Leiden models. In their article (Almeida-Paulo et al.) [1], linear regression limited sampling strategies for AUC<sub>12</sub> prediction were developed and not limited sampling maximum a priori (MAP) Bayesian estimation models. Linear regression limited sampling strategies are inconvenient in a way that it requires strict adherence to set times for blood sample collection which is almost impossible in clinical practice. Erroneous predictions will occur if the sampling times are not exactly as requested in the sampling protocol. In contrast, maximum a priori (MAP) Bayesian population pharmacokinetic models as we have developed in our recent article [2] are far more flexible and can handle sampling times which deviate from the sampling protocol without resulting in erroneous predictions. Although these models require more complex calculations and the development of a population pharmacokinetic model, we believe these models are superior to linear regression limited sampling formulas

when used in clinical practice. Currently different software packages are available to support these population pharmacokinetic models in clinical practice and have been evaluated recently [3]. Furthermore, different more user friendly web-based initiatives are emerging such as Dose Me [4] and Insight-rx [5]. In our University Medical Center, we have used these kinds of models for over a decade in routine clinical practice for prediction of cyclosporine, tacrolimus, and mycophenolic acid exposure for all renal and liver transplant recipients with satisfactory results. Furthermore, Størset et al. [6, 7] recently showed that computerized dose individualization improved target concentration achievement of tacrolimus after renal transplantation potentially improve long-term outcome. We agree with Dr. Antonio J. Carcas-Sansuán that hard evidence that AUC<sub>12</sub> monitoring of tacrolimus is superior to trough monitoring is still lacking when looking at clinical endpoints. However, based on theory and examples from clinical practice, we strongly believe that AUC<sub>12</sub> monitoring of tacrolimus is more informative and accurate and should therefore be applied. The development of dried blood spot techniques [8, 9] has also made the limited sampling AUC<sub>12</sub> for patient less burdensome because the blood sampling can now be performed at home. To gain more evidence with respect to improvement of clinical outcome using these models, we would suggest to set up a two arm randomized clinical trial in a high acute rejection risk patient population to evaluate the differences in acute rejection episodes and renal function decline over a period of for instance 5 years between the trough monitoring arm and the limited sampling AUC<sub>12</sub> monitoring arm. Such a study would be able to provide indisputable evidence for potential additional value of AUC<sub>12</sub> over trough monitoring; however, it will be challenging to finance such a study with a high sample size and long-term follow-up.

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