

**To the Editor:**

We appreciate the opportunity to respond to the comments of Saint-Marcoux et al. about our article that published in the April 2005 issue of *Therapeutic Drug Monitoring*.<sup>1</sup> The ability to use sparse data that may not have been collected for the specific purpose of pharmacokinetic modeling is one of the advantages of the population approach to analysis. This was the case in our analysis, in which the data came from a randomized, clinical study designed to address the variability in pharmacokinetics of two cyclosporine dosage forms and its relationship with the clinical outcomes after cardiopulmonary transplantation.<sup>2</sup> Not unexpectedly, as pointed out in our article, the data did not allow us to perform a detailed and comprehensive analysis of cyclosporine's pharmacokinetics. Specifically, the lack of information during the period immediately after a dose prevented us from fully characterizing absorption and distribution of cyclosporine. The focus of our analysis was to estimate apparent clearance and investigate potential patient covariates for this parameter. The simplest published models, first-order absorption with no lag time and a one compartment model, were used for absorption and distribution respectively. The value for the absorption rate constants were not selected arbitrarily, but fixed to published population average values found in the literature.<sup>3</sup>

The sparse nature of our data was balanced by the number of profiles that were available for analysis. Specifically the 335 abbreviated profiles allowed us to follow the patients during a 12-month

period and address inpatient variability in apparent clearance.

Our final model enabled us to account for some of the variability in cyclosporine pharmacokinetics. Because we did not investigate nor evaluate variability in absorption and distribution, we did not expect our analysis to provide an almost complete account of cyclosporine's variability. We fully concur with the call of Saint-Marcoux et al. for more analyses using richer data spread throughout a dosing interval. Unfortunately, in clinical practice the ideal is not always available and a compromise often has to be made between a rich, diverse real patient group versus detailed concentration-time data collected throughout 1 dosing interval. We encourage further studies using rich data to balance our analysis.

On a final note, we advise Dr. Saint-Marcoux and colleagues to read our article more carefully before making comments, such as "it is surprising that none of the previously published popPK studies of oral cyclosporine in transplant patients were cited by Rosenbaum et al." Although it is not possible to refer to every single popPK paper on cyclosporine published in the literature, we referenced 5 such papers (references 14, 15, 16, 27, and 28), including 1 of the references that we have been accused of ignoring (Rousseau et al,<sup>4</sup> reference 16 of the article). Also in our article, the influence of cystic fibrosis (CF) on cyclosporine absorption was adequately referenced by including a more recent study by Tan et al<sup>5</sup> (reference 20) than the one requested by Saint-Marcoux et al.<sup>6</sup>

The earlier article<sup>6</sup> only included CF patients on Sandimmune formulation, whereas the one referenced,<sup>5</sup> included data obtained from CF patients being switched from Sandimmune to Neoral formulations of cyclosporine, which was more pertinent to our article.

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