LETTER TO THE EDITOR

Authors' reply to Ekberg *et al.* 'no robust conclusions to be drawn from clinical trials in the absence of an adequate control group'

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We read with interest the Invited Commentary by Ekberg and Meier-Kriesche [1] concerning our recent article presenting the 12-month findings from two multicenter studies of concentration controlled everolimus in *de novo* renal transplant recipients [2].

The development program to assess the efficacy and safety of everolimus has been extensive, involving over 6500 transplant patients, and still continues today. By considering our report on the 12-month results of the 2306 and 2307 studies in the context of the overall development program, many of the concerns raised by Drs Ekberg and Meier-Kriesche are resolved. Two large 3-year prospective multicenter studies including over 1100 patients compared fixed everolimus 1.5 and 3 mg/day versus a mycophenolate mofetil (MMF) control arm. All three arms utilized standard-exposure cyclosporin (CsA) and confirmed that everolimus as part of the combination therapy prevented acute rejection [3–5]. A subsequent pilot study demonstrated that renal function can be preserved when everolimus was administered with low-dose versus standard-dose CsA [6]. However, additional data supported that the regimen might be further optimized when everolimus levels were guided by drug level monitoring, and attention accordingly turned to demonstrating the safety and efficacy of concentration controlled everolimus with a low-dose CsA regimen. Thus, the studies described in our article (2306 and 2307) were undertaken with this clear objective [2,7]. Given the contemporaneous nature of the 2306 and 2307 studies to the large phase III controlled trials and since the clinical management of renal transplant subjects had not evolved in the limited period of time, the comparison of the results across these trials was a reasonable and clinically relevant strategy to describe the safety and efficacy of concentration controlled everolimus with reduced levels of CsA.

We agree that continued investigations in preservation of renal function with various combination therapies are still a key interest in the transplantation community. Accordingly, a new multicenter prospective global study is being undertaken to compare low-dose CsA regimens with everolimus with a control arm of MMF with standard-dose CsA.

A further point raised by your correspondent was that the exposure to CsA in studies 2306 and 2307 could not be considered low. These trials used C_2 monitoring of CsA, a more sensitive monitoring strategy than conventional trough monitoring [8], and the C_2 levels achieved were lower than those reported in routine practice around that time [8]. Compared with patients in the large controlled trial who received everolimus with standard-dose CsA [4], for example, CsA trough levels were approximately 57% lower in the 2306 trial (both studies were induction-free) [2,9].

In summary, we believe that the data from these studies have provided new insights into the concurrent use of everolimus with lower exposure CsA as well as a deepening of our clinical experience with a new immunosuppressant that has become an additional choice for the clinician in management of the renal transplant recipient. We expect ongoing studies on combination therapies (including other CNI's) with everolimus will further define optimal dosing and regimens in transplantation.

Helio Tedesco-Silva[1] and Julio Pascual[2]
1 Division of Nephrology, Hospital do Rim e Hipertensao, Sao Paulo, Brazil
2 Department of Nephrology, Hospital Ramon y Cajal, Madrid, Spain

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