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INVITED COMMENTARY

No robust conclusions to be drawn from clinical trials in the absence of an adequate control group

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It is not difficult to agree with Tedesco *et al.* that important strategies for immunosuppression at this time include the reduction of calcineurin inhibitors (CNIs) to minimize nephrotoxicity and maximize graft function and survival. However, in their report of two studies on 'everolimus with reduced exposure cyclosporine' in this issue of Transplant International [1], we find a number of concerns that warrant some comments.

The focus of interest is nephrotoxicity. Although, everolimus may be a non-nephrotoxic alternative, it is a well-known fact that target of rapamycin (TOR) inhibitors like everolimus and sirolimus may potentiate the nephrotoxicity of CNIs and, in particular, cyclosporine A (CsA). Sirolimus combined with CsA was found in earlier studies to be associated with worse renal function compared with CsA combined with mycophenolate mofetil (MMF), and the same combination was later shown to have worse graft survival compared with standard regimens in both randomized prospective and large retrospective studies. Consequently, in the United States, the use of the sirolimus and CsA combination in renal transplantation has declined in clinical practice [2]. It is therefore unclear how these studies, in the absence of a suitable control group, can address concerns about the combined nephrotoxicity of everolimus and CsA. In the absence of an adequate control group, conclusions about efficacy, but more importantly about safety of the protocol, are impossible.

The declaration of Helsinki formulated and periodically updated by the World Medical Association [3] clearly states that 'The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists'. This stands to reason because the same association also states that 'Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research', and even if at inception of a clinical trial there is consensus that the tested regimen might benefit the population, this assumption has to be monitored throughout the trial by a safety monitoring board comparing the accumulating data with a control group that is receiving 'the best current prophylactic, diagnostic, and therapeutic methods'.

It is therefore unclear why the design of the two studies reported by Tedesco *et al.* did not include an appropriate control group, for example, with CsA and MMF. Uncontrolled trials are of the lowest caliber or quality because of the biases and lack of rigor that are inherent in such studies. Moreover, the inability to compare one group with another means that the study results are of no value in the assessment of a drug's effectiveness and comparative safety. For these reasons, the 'safety and efficacy of everolimus with reduced exposure cyclosporine' advocated in the title of the report by Tedesco *et al.* cannot be established by the two trials described.

The title of the report by Tedesco *et al.* claims that the exposure of CsA was reduced. In Table 3 of their report [1], the CsA dose, concentration 2 h after dosing (C_2) and trough levels from month 4 to 12 are presented. Admittedly, the mean trough levels of CsA during this

period of time are low, below 100 ng/ml. However, in a previous publication of the 6-month results of the same two studies [4], in Study 1, it was evident that the CsA C_2 targets of 1200, 800, and 600 ng/ml during the first 3 months, respectively, resulted in mean CsA trough levels of 239 and 278 ng/ml in the two everolimus (1.5 or 3.0 mg daily) treatment groups before they were later reduced. These are generally not considered low levels of CsA exposure. In Study 2, the observed initial trough levels of CsA were lower (141 and 136 ng/ml), but still cannot be considered low.

In addition, the title of the earlier 6-month publication of the same two studies [4] did not state reduced dose of CsA but 'optimized CsA dosing', referring to C_2 monitoring. This is also the theme of a large part of the discussion in both publications, reported as a main finding, with the argument that C_2 monitoring leads to lower doses and improved renal function. C_2 monitoring may be an improved method of assessing CsA exposure, but does not in itself determine whether the level of the exposure may be high (as in Study 1) or reduced (as in Study 2). The same limitations about study design mentioned above also apply to the C_2 monitoring. It was hypothesized in the trial designs that C_2 monitoring with everolimus would optimize renal function, but no control group was planned to test this hypothesis raising questions about the conclusions of the earlier 6-month publication, and more importantly about its safety with respect to an appropriate treatment control [3].

Delayed onset of transplant function (DGF) was an exclusion criterion in Study 2. This exclusion criterion may be controversial as in this study, patients had reduced doses of CsA (half of the C_2 levels in Study 1) with basiliximab induction; a regimen that may be optimal for patients with DGF. It would have been more logical to exclude patients with DGF from Study 1. This raises certainly a concern about the comparability of the two studies. Despite being an exclusion criterion, about 20% of the patients had DGF in Study 2. It is unclear why these protocol violations were allowed and patients not withdrawn.

Moreover, black patients were enrolled ($n = 15$ and $n = 13$ in the two studies, respectively) but were not randomized; all black patients were given the high dose of everolimus (3 mg). They were not included in any overall analysis, but still they were included in the report of demographics (Table 1) [1,4]. It is not clear why these patients were handled in this way; either they were subjects to test the hypothesis or they were not. They were obviously not.

The primary endpoint was renal function, assessed by calculated glomerular filtration rates according to both Nankivell and Cockcroft–Gault formulae, and also by serum creatinine level. From these primary endpoints, serum creatinine was chosen for use in the sample size calculation. A clinically relevant difference of 25 μmol/l between the two treatment arms (1.5 or 3.0 mg everolimus daily) was chosen and sample sizes calculated as 216 non-black patients per study, a rather small number of patients. There were no significant differences found; serum creatinine levels and calculated GFRs were virtually the same at all time points in the two groups in both studies.

Consequently, the reduced CsA exposure in Study 2 did not result in improved levels of renal function as compared with Study 1. This is, however, scientifically not a correct conclusion; it is based on a comparison between two separate studies. It is misleading that the two studies are reported in the same paper. A correct conclusion would be that renal function was not different comparing regimens including either a high or a low dose of everolimus (1.5 mg or 3 mg), neither when tested with a high nor reduced dose of CsA (the latter being combined with basiliximab in one study). These are the main findings of the two studies, at 6 months as well as at 12 months. The argument for the Tedesco *et al.* publication [1] in addition to the earlier 6-month publication [4] was that it is important to evaluate whether the conclusions remain valid with time. In brief, we may say that they do, but whether any of these approaches provided the safety and efficacy advocated can certainly not be answered by these studies.

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