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INVITED COMMENTARY

Risks and benefits of everolimus

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In the current version of this journal, Ferreira *et al.* [1] report the outcome of a 12-month, prospective, randomized, controlled trial from Sao Paolo, Brazil comparing mycophenolate (MPA) and everolimus in low/standard risk, *de-novo* kidney transplant recipients from extended criteria deceased donors (donor age >60 years, mean kidney donor profile index 89). All patients received standard steroids, up to 4 days of 1.5 mg/kg ATG induction and delayed introduction of low-dose (0.05 mg/kg BID) tacrolimus aiming at trough levels between 3 and 5 ng/ml (median level in everolimus arm was 5 ng/ml vs. 5–6 ng/ml in MPA arm). The authors randomized 171 patients to either everolimus (n = 88, 1.5 mg BID, aiming at trough levels of 4–8 ng/ml) or MPA (n = 83, 720 mg BID). The study highlights the risks and benefits of everolimus and is an example for the general dilemma in transplantation between under-immunosuppresion (= rejection) and overimmunosuppression (=infection).

According to last international CMV consensus guidelines [2], universal prophylaxis and preemptive therapy are both recommended in patients with intermediate CMV risk. Because of reimbursement issues in Brazil for the expensive valganciclovir prophylaxis, drug-related side effects, and only 6% CMV high-risk patients, the Sao Paolo group explored the option of a preemptive CMV treatment strategy with tight CMV monitoring together with the use of mTOR inhibitors [1,3]. The observation of lower CMV infection rates under mTOR inhibitors compared with MPA dates back from early clinical trials [4] and was confirmed in recent trials [3,5,6] and meta-analyzes [7–10].

The incidence of delayed graft function (DGF; defined as one or more dialysis in the first week post-transplant) was high (on average 69%) despite delayed introduction of tacrolimus, questioning the benefit of delaying tacrolimus. As expected, patients receiving everolimus had an 89% risk reduction of CMV (13.6% vs. 71.6%) at 12 months compared with MPA. However, all other outcome parameters such as rejection (16% vs. 5%), treatment discontinuation (40% vs. 28%), kidney function (32 vs. 43 ml/min), duration of DGF (6 vs. 4 days), graft loss (11% vs. 1%), and death- (10% vs. 1%) favored MPA, and the study was terminated prematurely due to poor outcomes and safety concerns in the everolimus arm.

What are the lessons from this trial?

Obviously, the combination of MPA and tacrolimus remains the standard of care for patients receiving kidneys from extended criteria donors, despite higher incidence of CMV infections. The current trial demonstrates, that CMV infections, although frequent in MPA-treated patients, can be managed successfully, while the use of everolimus is far more challenging,

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even in an extremely experienced and large center, such as Sao Paolo. In this study, the problems with the use of everolimus started right after transplantation with longer DGF duration, wound-healing issues requiring surgical interventions, and more rejections due to difficulties in reaching adequate early everolimus exposure. This trial adds further evidence to previous observations [11], which are summarized in the recommendation from a recent consensus conference [12], that everolimus levels >3 ng/ml are crucial for sufficient rejection prophylaxis.

Besides underimmunosuppression, typical drug-related side effects (hyperlipidemia, stomatitis, edema, proteinuria, wound-healing, and lymphoceles), remain a major concern in everolimus-treated patients, leading to frequent discontinuations. All clinical trials [1,3–6,13] and recent meta-analyzes [7–10] clearly demonstrate inferior tolerability of everolimus compared with MPA, as evidenced by higher discontinuation rates due to adverse events. Contrary to everolimus, MPA has a wide therapeutic range. By far most MPA-associated side effects such as leucopenia, gastrointestinal problems, and viral infections are managed sucessfully by dose reductions and/or concomittant treatment. In contrast, everolimus-associated side effects are more diverse and obviously more difficult to treat. Inexperience of the investigator and center differences may account for some of the observed differences, but 15 years after approval in Europe, even experienced investigators rather discontinue everolimus and switch to standard of care, than to manage the adverse event and continue everolimus, as evidenced by high discontinuation rates in recent large trials [1,3,5,6,13].

Finally, frequent rejections followed by intense rejection treatment, severe infections, and aggravated nephrotoxicity caused renal problems, graft loss, and death in this trial. Again, this trial, like many other clinical trials [1,3–6] and meta-analyzes [8–10] demonstrates, that renal dysfunction is more frequent in patients treated with combination of mTOR inhibitors and CNIs, especially if CNI levels are not adequately lowered [10–12,14]. A thorough pharmacodynamic analysis from a large registration trial [11] showed that already tacrolimus levels of 4 ng/ml increased the risk of low and/or decreasing renal function as early as 12 months post-transplant. In the ATHENA study [6], GFR of tacrolimus/everolimus combination was 7 ml/min lower compared with tacrolimus/MPA, most likely due to inadequate high tacrolimus concentrations of around 6 ng/ml. In the large TRANSFORM trial, GFR was 2.3 ml/min lower in CNI/everolimus combination therapy (tacrolimus levels around 4 ng/ml) compared to CNI/MPA with tacrolimus concentrations of 6–7 ng/ml. These data together with the current study [1], further support the results from the pharmacodynamic analysis [11], suggesting aggravated nephrotoxicity even at "low" tacrolimus levels. The observation of inferior renal function after only 1–2 years of everolimus/tacrolimus combination therapy is worrisome, as nephrotoxicity usually presents many years post-transplant, and no long-term data on the evolution of renal function are available for everolimus/tacrolimus combination therapy.

Thus, in summary, this trial together with the results of other recent data [1,3–11,13] provides further evidence, that MPA/tacrolimus remains current standard of care in de-novo renal allograft recipients, despite all the well known-limitations of this combination therapy. Everolimus is a well-proven second-line treatment option in case of MPA intolerability, such as severe viral infections, which are difficult to treat. Future research should aim to improve tacrolimus/MPA combination therapy with a focus on a reduction of side effects, and should aim to optimize the protocol for important subgroups such as patients receiving kidney from extended criteria donors, living donor transplants, elderly patients, and immunized recipients.

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Conflicts of interest

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