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Everolimus *versus* mycophenolate mofetil in liver transplantation: every improvement in renal function matters

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The current edition of the Journal features a Spanish, nationwide, multi-institutional study by Gomez Bravo MA et al. (1) exploring the advantages of everolimus (EVR)-facilitated tacrolimus (TAC) minimization versus TAC in combination with mycophenolate mofetil (MMF) after liver transplantation (LT).

The study backbone is derived from previous registration trials of EVR in deceased- (2) and living-donor LT (3), but the novelty here is that the authors used induction agents (anti-IL2 receptor antibody (IL-2RA)) and randomized patients one month after surgery to initiate EVR in combination with reduced-exposure TAC (≤ 5 ng/mL) versus TAC (6-10 ng/mL) + MMF until the end of study (52 weeks). This is one of the first attempts to compare prospectively two renal-sparing immunosuppressive schedules (EVR + TAC versus TAC + MMF) making use of the most largely implemented ingredients to reduce TAC exposure, i.e., IL-2RA, EVR, and MMF.

A further novelty — although one derived from studies in large cohorts of non-transplant patients — was the inclusion of the concept of *clinical benefit* when appraising the impact of EVR versus MMF on renal function (3). Clinical benefit was defined as a 1 to 2 range shift in the Kidney Disease: Improving Global Outcomes

(KDIGO) function categories over the study period for patients with more impaired renal function (30-59 mL/min/1.73 m^2) and stabilization for patients with higher estimated glomerular filtration rates (eGFR) at randomization (4). Although based on prognostic assumptions, this concept is however imperfect like any attempt to introduce strict mathematical models in clinical practice. Patients whose renal function values are close to range cut-offs (i.e., 56 mL/min/1.73 m^2) might be counted as clinical benefits from a 10 % increase as opposed to patients with more deteriorated kidneys (i.e., 40 mL/min/1.73 m^2) and experiencing similar function gains. As clinicians we know that the more severe (and chronically longer) is renal function deterioration, the more difficult is to get any improvement (5). This is one of the reasons leading to the exclusion of poor renal function LT candidates (usually below 30 mL/min/1.73 m^2) from renal-sparing immunosuppressive trials like the current one. In addition, the kidney attrition rate due to indications for transplantation, surgeries, blood transfusions, hemodynamic instability, co-medication, and use of nephrotoxic agents is difficult to capture through these formulae, which should be used with caution and filtered with seasoned clinical experience.

Even though the authors are to be commended for highlighting there was no difference in clinical benefit on renal function across the 2 arms one year after transplantation, the numerical gain in eGFR achieved by the EVR-facilitated TAC reduction was higher and statistically significant when compared to patients on TAC + MMF. This was due to a higher degree of TAC reduction for patients on EVR, ranging from 30 % at 2 weeks after randomization to 41 % at week 52. The potential is there that patients on EVR might show greater benefits in their renal function if the authors had the possibility to re-test eGFR at longer follow-ups.

Based on the study by Gomez Bravo et al., might we conclude that a policy of EVR-facilitated TAC reduction is equivalent to TAC + MMF? Probably not. Firstly, there is a plethora of studies confirming the feasibility and safety of TAC elimination starting 6-12 months after surgery for patients who were initiated on EVR in the *de novo* or maintenance settings for oncological or renal issues (6-10), and the number of reports far exceeds those on MMF monotherapy (11-13). This latter alternative, which was reported in the literature by Spanish authors among others, seems to be safer for well-

selected, longer follow-up patients (4-6 years after transplantation) (11,13), and requires longer weaning times if implemented earlier. In addition, the antiproliferative profile of mammalian target of rapamycin inhibitors (mTORi) makes EVR a more appealing drug to reduce the risk of *de novo* malignant disease (14) and recurrence of hepatocellular carcinoma (15). In clinical practice, it would be likely that TAC be tapered as early as 6 months after transplantation for patients on EVR, while patients on MMF would require TAC for the first 4-6 years after surgery, albeit with gradually reduced exposure. Thus, patients on EVR might derive a twofold advantage from their mTORi-incorporating immunosuppressive regimen: a numerically greater increase in renal function and earlier TAC withdrawal, both highlighting different efficacies and mechanisms of action for mTORi versus antimetabolites.

Secondly, the safety profile of either schedule was somewhat different, with patients on EVR experiencing more peripheral edema, leukopenia, thrombocytopenia, and dyslipidemia but less cytomegalovirus (CMV) infection than their MMF counterparts (1). The issue of a numerically higher incidence of diabetes mellitus (34.0 % versus 22.0 %; p = 0.051) for EVR patients requires clarification, and should be interpreted with caution in light of the indications to transplantation, incidence of rejection, and use of corticosteroids across the 2 study arms (1).

One crucial issue the study failed to address was the treatment of patients with poor renal function at transplantation, critically ill transplant candidates, and those with rapidly deteriorating eGFR after surgery (e.g., run-in failures). These categories are usually left out from comparative, randomized studies, and usually referred to empiric immunosuppression schedules derived from clinical experience and based on staggered TAC introduction and combination of IL2RA, MMF and steroids. Future studies should explore the best strategies to circumvent TAC or replace signal-1 inhibition in these patients, due to side effects of calcineurin inhibitors. Ten years after the introduction of EVR (2), little progress has been made in this direction.

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