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Editorial 5836 inglés

Protecting renal function: a relevant decision for liver transplantation

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Advances in surgical technique, as well as in medical management and immunosuppression (IS), have represented a significant improvement in the survival of patients undergoing liver transplantation (LT), with 1-year, 5-year, and 10-year survival rates of 86%, 73%, and 62%, respectively, according to the Spanish liver transplant registry (1).

Development of renal dysfunction is common in LT, and has a relevant impact on morbidity and mortality. The extent of renal function impairment is associated with a higher risk of mortality, cardiovascular complications, and prolonged hospital stay in the general population (2) and in patients with renal (3) or liver transplant (4). In LT patients mortality increases when dyalisis is required (5) as compared to patients undergoing kidney transplantation for chronic kidney disease (CKD) (6). In some relevant series renal failure was the cause of death for 10% of patients beyond 5 years after LT, and CKD-related deaths were seen to progressively increase over follow-up (7).

In the immediate post-liver transplantation period a varying proportion of LT patients –from 5% to 50%– develop acute kidney injury (AKI), and most patients who develop CKD do so within 9 months after LT. Pawarode et al. (8) defined CKD as a decrease in glomerular filtration rate (GFR) greater than 30 mL/min/1.73 m^2 below baseline, and severe CKD as a GFR lower than 30 mL/min/1.73 m^2, and found that 35% of LT patients surviving beyond 6 months developed CKD, with a cumulative incidence of 41% at 5 years. Furthermore, 7% develop severe CKD with a cumulative rate of 8% at 5 years. In this study, as in others, pre-transplant creatinine levels above 1.2 and baseline GFR

were determinants of CKD, and GFR < 30 mL/min/1.73 m^2 at 3 months was more likely to predict severe CKD. These same risk factors were confirmed in the large study by Ojo (4), where 26.8% of patients with LT already had a GFR lower than 60 before transplantation. In this study the rates of CKD (GFR < 30 mL/min/1.73 m^2) at 12, 36, and 60 months were 8%, 13.9%, and 18.1%, respectively. The wide differences in CKD rates observed among series result from the use of varying criteria for the definition of CKD and different follow-up periods.

In this issue of *The Spanish Journal of Gastroenterology (Revista Española de Enfermedades Digestivas)*, Herrero et al. (9) discuss the evolution of renal function from the sixth month post-LT and over a period of 30 months in LT patients with preserved renal function at LT (GFR ≥ 60 mL/min/1.73 m^2 and no evidence of renal damage). Considering the concept of CKD as defined in the KDIGO guidelines, that is, as a GFR lower than 60 mL/min/1.73 m^2, in the study by Herrero et al. the rate of stage-III CKD at 2 years was 26.4%, and that of stage-IV CKD was 0.5%. Few studies are available for comparison with the Spanish series because of varying CKD definitions and follow-up periods, and of CKD stratification other than GFR below 60 mL/min/1.73 m^2 (stages III, IV, and V). In a recent study by Allen et al. (10) the rate of stage-III CKD at 1 and 5 years was 50% and 49%, respectively, and that of stage-IV CKD was 4% and 5%, respectively; these figures are clearly higher, even at 1 year, than those described by Herrero et al., namely 30.8% at 1 year and 26.4% at 30 months for stage III, and 0.5% for stage IV within both periods (9). Furthermore, the percentage of patients with GFR ≥ 60 mL/min/1.73 m^2 (CKD stages I and II) was 42% and 32% at 1 and 5 years in the series by Allen et al., hence clearly lower than in the Spanish series, where rates of 68.8% and 73.1% at 1 year and 30 months, respectively, are reported. Although Allen et al. do not report on IS type or level, a clear difference between both studies lies in the percentage of patients undergoing transplantation with a GFR lower than 60 mL/min/1.73 m^2 before LT, which was 27% in the series by Allen et al. *versus* 0% in the series by Herrero et al. The study by Allen et al. also found a very interesting result, namely an increase in mortality rate dependent upon GFR; thus, death risk rises nearly three times for a GFR of 15-29 mL/min/1.73 m^2, and up to 5 times for GFR levels lower than 15 mL/min/1.73 m^2 (10). As discussed by Herrero et al. (9), a greater number of

patients with renal function impairment pre-transplantation, together with a higher usage of calcineurin inhibitors (CNIs), may have contributed to greater renal function impairment in the large series by Ojo (4), and may also account for the differences found with the series by Allen et al.

Several factors contribute to CDK risk in LT and other non-renal organ transplantations (11, 12). These include unidentified CKD prior to LT (patients with high blood pressure, diabetes mellitus, HCV, older age, etc.) –it may be overlooked when serum creatinine is used as renal function marker– and also acute renal damage pre-transplantation and peri-transplantation. CNIs are no doubt nephrotoxic and primarily contribute to CKD development and progression in LT patients. However, differences in renal function evolution results between LT series, both in prospective, randomized clinical trials and observational studies, may depend on multiple differential factors related to study population characteristics (DM, HBP, age, etc.) and both intra- and post-operative complications such as CNI management. Notwithstanding this, the use of CNIs markedly contributes to renal damage, albeit the cause of CKD after LT not always is CNI-related nephrotoxicity, which varies among the low number of series where a renal biopsy was collected (13, 14).

The fact that IS levels and higher cumulative CNI doses represent a risk factor for CKD in LT is clear, and tacrolimus doses of 6-10 ng/mL are recommended within the first month after LT (15, 16). Several strategies may reduce CNI-related nephrotoxicity since the immediate post-LT period, or improve renal function following impairment (17). Such strategies include: minimizing CNI use since the immediate post-LT period (18) or long-term following renal function impairment, and using mycophenolate mofetil (MMF) (19) or everolimus (20) without NCIs or with IS discontinuation (21). We should bear in mind that renal function improvement following CNI discontinuation and conversion to monotherapy with MMF largely depends on conversion timing (improvement decreases with time) and on the rate of GFR impairment over the previous two years, with improvement being poorer for faster impairment and lower GFR level (worse for GFR < 40) (22).

In analyzing the paper by Herrero et al. we may find three key items that account for their excellent renal function outcomes in the long term: all patients had good renal

function before transplantation, tacrolimus levels remained stable and moderate through follow-up, and CNI levels were possibly minimized in patients with impaired renal function. The latter aspect is reflected by ongoing GFR improvements in the group of patients where CNIs were combined with non-nephrotoxic IS agents (MMF, everolimus). This attitude possibly applies to a vast majority of Spanish LT teams, where the tendency to IS minimization is universal (23).

In summary, renal function impairment in LT is dependent on pre-, peri- and post-LT factors, with adequate IS, particularly CNI, management being a key component. Therefore, we must follow available recommendations to protect renal function in LT patients, which include appropriate IS management –IS should be kept at a minimum from the outset, and conditions such as hypertension and diabetes mellitus should be adequately managed.

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