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Michel Rayar, Edouard Bardou-Jacquet

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Michel Rayar[1,2], Edouard bardou-Jacquet[2,3]

[1] : Univ Rennes, CHU Rennes, Service de Chirurgie Hepatobiliaire et Digestive F-35000 Rennes, France

[2] : Univ Rennes, INSERM, CHU Rennes, CIC 1414 (Centre d'Investigation Clinique de Rennes), F-35000 Rennes, France

[3] : Univ Rennes, CHU Rennes, Service des Maladies du Foie, F-35000 Rennes, France; edouard.bardou-jacquet@chu-rennes.fr

Dear editor,

We read with great interest the study of Montano-Loza et al[1] regarding outcomes after liver transplantation for primary biliary cholangitis (PBC) and factors associated with its recurrence. We first want to congratulate the authors for their work reporting the largest multicentric cohort published, allowing the identification of risk factors of PBC recurrence like young age at liver transplant, presence of biochemical markers of cholestasis after transplant, and use of tacrolimus.

However, regarding the impact of the immunosuppressive drugs, we believe that the authors' conclusions might benefit from further analysis.

Indeed, tacrolimus seems to be associated with a higher risk of PBC recurrence compared to cyclosporine in univariate analysis (Kaplan-Meier curves with log-rank test) with a higher 5-year recurrence rate of 28% vs 11% ($p<0.001$). This finding was confirmed by the univariate Cox analysis with a hazard ratio (HR) for tacrolimus of 2.31 ($p<0.001$) and 0.62 ($p=0.001$) for cyclosporine, suggesting a protective effect of cyclosporine compared to tacrolimus. However, in multivariate analysis, all immunosuppressive drugs have a HR higher than 1 suggesting that other factors associated with the use of cyclosporine mitigate its putative protective effect. A significant p-value was observed only for tacrolimus and mycophenolate mofetil. Regarding cyclosporine the p-value did not reach significance ($p=0.052$ in model 1 and $p=0.07$ in model 2) maybe because of a lack of power (i.e. 28% of patients had cyclosporine).

As all drugs have an HR superior to 1 (taking as reference the absence of this drug) in multivariate analysis, they could be considered as risks factors for recurrence and therefore one could conclude that the absence of immunosuppressive drugs may prevent PBC recurrence. However, an immunosuppressive drug regimen is mandatory after liver transplant and usually includes a main drug (mostly a calcineurin inhibitor) and often a second drug.

We believe that this misinterpretation could be prevented by further statistical analysis of the available data.

Indeed, the main immunosuppressive drugs should be compared to each other and entered in the multivariate model as a unique categorical variable with different modalities (i.e. tacrolimus or cyclosporine or other drugs) allowing calculation of an HR and a p-value for each drug in comparison to one drug (which will be considered as reference treatment with a HR=1). A second categorical

variable could be set up to take the second line immunosuppressive drug into account. This would provide a clearer idea of the potential benefit of each immunosuppressive regimen. If the main immunosuppressive therapy changed during the first year, this categorical variable should be analyzed as a time dependent covariate in the multivariate cox model.

We hope that clarifying this point may allow the authors to provide clear recommendations regarding the best immunosuppressive regimen for these patients.

Reference:

1: Montano-Loza AJ, Hansen BE, Corpechot C, Factors Associated With Recurrence of Primary Biliary Cholangitis After Liver Transplantation and Effects on Graft and Patient Survival. Gastroenterology 2019;156:96–107