Tolerance After Liver Transplantation: Where Are We?

TO THE EDITOR:

We have read with great interest the review article by Feng and Bucuvalas.[1] They reviewed from a molecular to a clinical point of view all aspects regarding immune tolerance (IT) after liver transplantation (LT), including all available evidence, comprising adult and pediatric, retrospective and prospective studies, clinical trials, and even the different IT contexts (operational or induced). The success rate of immunosuppression (IS) withdrawal in these studies varied between 6% and 63%, but was usually approximately 20%-30%.

The biggest Portuguese adult LT unit recently reached its 2000th LT. Although there are anecdotal cases of patients "involuntarily" going without immunosuppression (for reasons such as patient's unwillingness to take medicine or unacceptable adverse effects), a program of IT has not yet been designed. Therefore, it would be interesting to think about how to implement such a program in a "real life" setting, outside the context of a clinical trial.

On the basis of the information reviewed in their article,[1] namely, the 12 single-center and 2 multicenter reports on adult operational IT, we propose a methodology in a real life setting of selection and evaluation of results that would probably improve the only moderate outcomes seen until now. One important aspect is that patients should have been transplanted for >3 years, although the most favorable results are seen with >10 years of LT.[2] If the patient is <50 years, probably more time of transplantation should be required; in the Liver Immunosuppression Free Trial (LIFT) (NCT02498977) conducted by Sanchez-Fueyo that is currently enrolling, they propose >6 years. Another aspect is that patients with autoimmune hepatitis and probably hepatitis C infection (because it is associated with more fibrosis) should be excluded. Finally, it should also be considered as inclusion criteria for normal liver tests, ferritin >30 ng/mL, and a liver biopsy with absence of acute or chronic rejection, portal inflammation in <50% of portal tracts (unless attributable to hepatitis C infection), central perivenulitis in <50% of central veins, METAVIR stage I or II, and hepatocyte iron accumulation. Patients may have been transplanted either with deceased or living donor organs because there are not sufficient data to affirm that 1 strategy is better than the other. After IS withdrawal, patients could be given regular liver tests (eg, every 3 months) and at 12 months after discontinuation, a liver biopsy would be performed. If there were no alterations at this point, the patient could continue off IS with frequent monitoring and maybe have a liver biopsy 3-5 years later. If there were characteristics suggestive of rejection or pronounced inflammation or fibrosis, the patient should restart IS.

We hypothesize that with aging and increased incidence of hepatocellular carcinoma and its improved survival rates, there may be a larger subset of patients who will be eligible for operational IT.

This empirical methodology could be further optimized once studies on biomarkers and IT inductioninterventions show good results and become available.

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