

Does the Liver Provide Immunosuppressive Advantage?

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Since the 1980s, there have been substantial improvements in survival after liver transplantation (LT), and advances in immunosuppressive therapy (IST) are largely responsible for these successes. Despite these achievements, LT recipients are burdened with lifelong IST, thereby incurring health care costs and the risks of side effects, infections, *de novo* malignancy, cardiovascular events, and chronic kidney disease.^{1,2} As such, outcomes for patients could be enhanced if IST exposure could be minimized or even eliminated after LT. Fortunately, the liver has immunoregulatory properties that can allow for select recipients to withdraw immunosuppression and require less IST in combined liver/other organ transplantation. This review discusses basic and clinical concepts of LT tolerance and situations in which the immunosuppressive advantage can potentially translate into improved outcomes.

BASIC AND CLINICAL EVIDENCE FOR HEPATIC TOLERANCE

The liver itself is the most immunoregulatory organ transplanted; it contains a high number of extramedullary

hematopoietic cells and a large mass of nonimmunogenic cells, and secretes a variety of immunoregulatory proteins (Fig. 1). The abundance of resident regulatory T cells and immature antigen-presenting cells appears to be protective of graft rejection. Clonal deletion of alloreactive immunocytes, inhibition of alloantibody effects, mixed donor-recipient hematopoietic chimerism, and immunological senescence are also hypothesized components of liver immunoregulation. Moreover, the graft itself may be considered the source of persistent tolerogen over being a stimulus and target for immune destruction. Early animal studies revealed that most mouse strains and outbred pigs spontaneously accept liver grafts without the need for immunosuppression, although this is not the case in skin and other organs of higher immunogenicity.³ In addition, in basic studies, the addition of a liver in the transplant procedure provides immunological protection of other organs (skin, heart, kidney) in combined transplantation.⁴ Early reports from Calne et al.^{5,6} of LT in pigs demonstrated an immunoprotective effect of the liver on rejection of a simultaneously transplanted non-hepatic organ.

Abbreviations: ACR, acute cellular rejection; DDLT, deceased donor liver transplantation; DSA, donor-specific antibody; IST, immunosuppressive therapy; LDLT, living donor liver transplantation; LT, liver transplantation.

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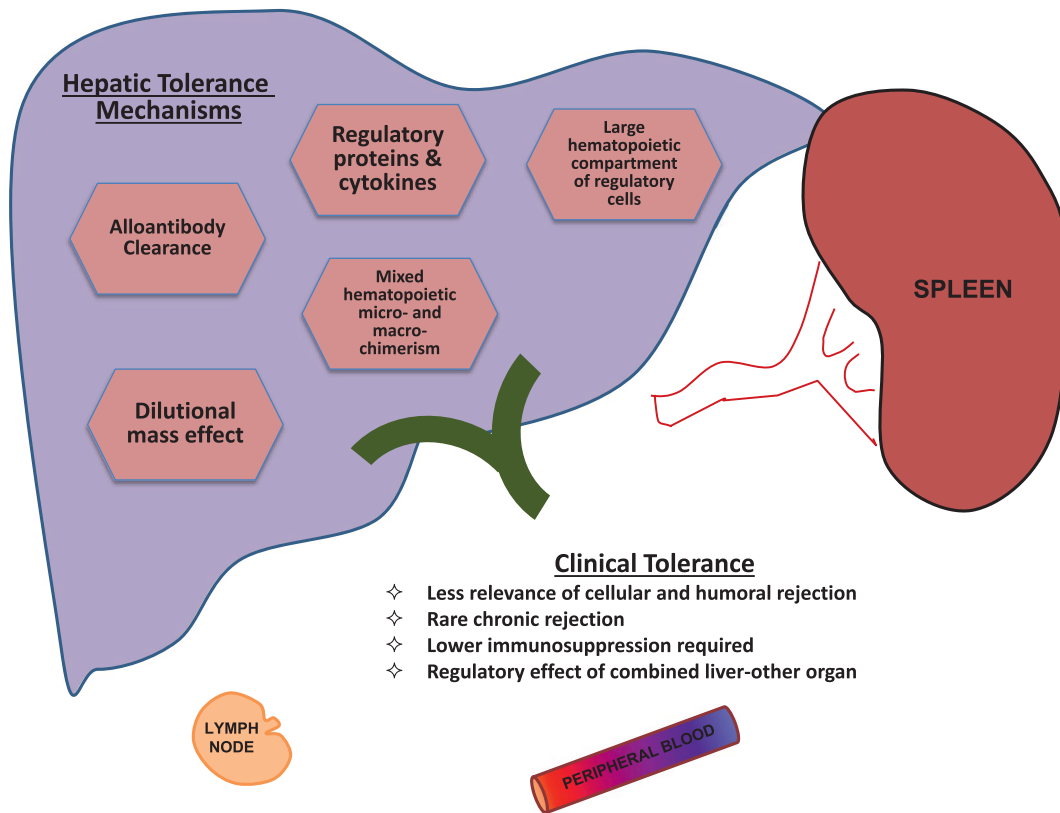


FIG 1 Mechanisms of and clinical evidence for hepatic tolerance.

In contrast with other solid organ recipients, LT recipients demonstrate clinical evidence supporting these immunoregulatory phenomena: the lower significance of human leukocyte antigen matching and rejection, incidence of chronic rejection, and amount of initial and maintenance IST required. Similar to animal studies, the liver appears to provide some level of immunological protection of other organs in combined human organ transplantation and is generally less adversely impacted by donor-specific antibodies (DSAs).⁷⁻⁹

IMMUNOSUPPRESSION WITHDRAWAL IN CLINICAL LT

Several studies, mostly single-center studies, have demonstrated the feasibility of IST withdrawal in select LT recipients, further supporting the concept of the liver providing immunosuppressive advantage.¹⁰ Overall, withdrawal has been successful for about 20% to 30% of patients (range 5%-70%), which is significantly higher than other organ transplants. At this point, the main predictors of success are absence of significant inflammation on initial biopsy

before withdrawal, older age, and a longer time from transplantation.¹¹ Fortunately, the development of acute cellular rejection (ACR) within the highly monitored clinical trial setting does not appear to negatively affect liver allografts, because most episodes have been diagnosed early when ACR is histologically mild and responsive to escalation of baseline IST. Overall, although of unclear clinical benefit, available literature strongly suggests that attempted IST withdrawal in appropriately selected and compliant patients in monitored research studies is reasonably safe.

IMMUNOLOGICAL ADVANTAGE OF LIVING DONOR LT

Although clinically less proven, the living donor liver transplantation (LDLT) procedure may provide an environment favoring tolerance over alloreactivity. This may be due to a less inflammatory operation because of significantly less ischemia in a more controlled setting, as well as biological similarity between donor and recipient. Evidence for LDLT providing further immunosuppressive advantage

are as follows: (1) generally higher IST withdrawal rates in LDLT versus deceased donor liver transplantation (DDLT), although there are no head-to-head studies¹⁰; (2) lower impact (rejection, graft survival) of DSAs in LDLT versus DDLT¹²; and (3) lower rate of biopsy-proven ACR in biologically related LDLT versus other donor-recipient combinations.^{13,14} Thus, there may be more opportunity in LDLT to conduct controlled tolerance studies with higher success, particularly when initiated at the time of or soon after LT.

IMMUNOLOGICAL ADVANTAGE OF COMBINED LIVER/OTHER ORGAN TRANSPLANT

Perhaps the best evidence for hepatic immunological protection is the lower rejection rate when a non-hepatic organ (kidney, heart, lung) is combined with a liver transplant. Taner et al.¹⁵⁻¹⁷ performed a number of studies demonstrating that the simultaneous liver graft is a key predictive factor of lower cellular and antibody-mediated rejection and renal function decline in kidney transplants, and that simultaneous liver-kidney (SLK) recipients have lower circulating effector memory T cells, proliferative responses to donor cells, and frequency of interferon- γ -producing alloreactive T cells compared with kidney-alone recipients. In addition, performing a kidney transplant from a different donor after LT results in higher rejection than if they were combined, supporting the importance of biological similarity.¹⁸ However, the liver is not completely protective against non-hepatic transplant cellular and antibody-mediated rejection. Single-center data have shown higher antibody-mediated kidney rejection rates in patients with class II DSAs undergoing SLK, and that the overall rate of kidney rejection (all types) is approximately 20% in SLK, which is surprisingly high.^{19,20} The tolerability of each rejection may be higher than in kidney transplant alone in terms of renal graft loss, but data have shown that renal function in SLK recipients is somewhat worse over time for those with versus without history of rejection.¹⁹ Overall, the evidence supports at least a partial immunoprotective effect of the liver on other organs, supporting its “immunosuppressive advantage.”

CONCLUSION

It is clear that the liver provides a significant level of immunosuppressive benefit in basic studies and most clinical scenarios. Translating this to improvements in transplant outcomes (e.g., benefit of less immunosuppression,

protection of other organs) needs to be further studied and tested in prospective clinical trials.

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