Liver transplantation

Paul J Marotta MD

Liver transplantation (LT) is now a viable option for nearly all patients with end-stage hepatic failure. Graft and patient survival rates have reached very acceptable levels, with reasonably good patient tolerability of long-term immunosuppression. However, optimization of immunosuppressive regimens, to minimize toxicity while preventing rejection, remains a major challenge. As transplant physicians endeavor to function in the midst of a dwindling donor organ supply, treatment options such as living donor LT are becoming more popular, but not without significant practical and ethical concerns. In addition, with the worldwide burden of LT secondary to hepatitis C virus (HCV) infection, the design of an effective immunosuppressive and antiviral prophylaxis regimen is needed to ensure a minimal risk of rejection while also preventing HCV recurrence among infected LT recipients. Finally, renal dysfunction following LT is a common occurrence, one that is associated with comparatively poor patient survival and increased morbidity. Immunosuppressive regimens that avoid or reduce nephrotoxic calcineurin inhibitor (CNI) drugs, such as cyclosporine and tacrolimus, are under investigation but require validation in long-term controlled trials. This supplement to *The Canadian Journal of Gastroenterology* features review articles on four of the most pressing topics facing LT physicians today.

Steroids remain a widely used immunosuppressive option following LT, for induction therapy, maintenance therapy or antirejection treatment. The widespread metabolic range of these drugs, however, can lead to numerous toxicities in LT patients, such as hypertension, hyperlipidemia, post-transplant diabetes, metabolic bone disease and growth retardation. Even the short-term use of steroids can significantly compromise outcomes in some LT recipients who may experience recurrence of hepatitis B virus and/or HCV infection or hepatocellular carcinoma. With a range of effective new immunosuppressants such as mycophenolate mofetil and tacrolimus now available, strategies can be envisioned to reduce, withdraw and, in some cases, completely avoid the use of steroids following LT. Use of these regimens, however, may entail a significant risk of rejection episodes, and their feasibility and safety in LT recipients is currently under investigation. The review by Oberholzer et al in this issue (pages 5C-11C) provides an overview of current steroid avoidance strategies and their benefits and risks following LT surgery.

Also in this issue, Wall and Solano (pages 12C-18C) discuss the current situation pertaining to living-donor liver transplantation (LDLT), a recently introduced strategy aimed at alleviating the overwhelming demand on the liver donor organ pool. Despite its promise, LDLT has brought along with it a unique set of technical and ethical dilemmas that have been the focus of considerable debate. Concerns over potential health risks to the donor, following the elective donation of

the right lobe of the liver, are at the forefront of the discussion, especially in the wake of a recent, publicized donor death. Application of this operation may have been too rapid, and a lack of comprehensive, documented case data precludes an adequate estimate of risks. In addition, an established consensus on surgical methodology is lacking. Controversy surrounding the use of this procedure will thus continue to escalate, and the authors provide an informative discussion of the current issues surrounding DDLT in their review.

HCV is now the most common indication for LT worldwide, and, despite comparable short-term graft and patient survival to other LT indications, patients transplanted for HCV are at a considerable disadvantage over the long term. Reinfection is nearly universal, with 90% of transplant recipients having detectable HCV RNA. There is also a growing concern that HCV recurrence following LT is becoming more aggressive, the reasons for which remain elusive. The specter of HCV reinfection, potentially leading to graft failure, retransplantation or death, raises significant technical issues (eg, choice of antiviral treatments and/or immunosuppressive maintenance therapy) as well as ethical issues (eg, priority of HCV-positive recipients for limited donor organs). These and other issues pertinent to LT in the HCV-infected individual are discussed by Dr Paul Marotta (pages 19C-26C).

Another common cause of morbidity following LT surgery is renal dysfunction, which is addressed by Dr Marcelo Cantarovich (pages 27C-40C). Post-LT renal dysfunction and the need for hemodialysis has been associated with comparatively poor outcomes in liver recipients, and, although clearly multifactorial in etiology (eg, metabolic abnormalities, pre-existent renal disease, hepatorenal syndrome), the nephrotoxic effects of CNI drugs have emerged as a significant contributing and/or causative factor. Rigorous control over metabolic abnormalities and therapeutic drug monitoring of CNIs may aid in reducing the incidence of renal dysfunction following LT. In addition, as with steroid avoidance, the availability of newer, less toxic immunosuppressive drugs has allowed the design of alternative renal-sparing immunosuppressive regimens, such as those that withdraw, avoid or use low-dose CNIs following LT. At present, there is no clear consensus as to which intervention for renal dysfunction is best. Ideally, a maintenance regimen would provide effective, long-term, non-nephrotoxic rejection prophylaxis, without significant metabolic toxicity. Tolerance remains the 'holy grail' in LT, and experimentation in this area continues. A critical review of the risks and benefits of current renal sparing interventions following LT is presented.

Continued research and discussion on the topics highlighted in this supplement will enable more effective and productive interventions for our patients when LT is an option.

Multi-Organ Transplant Program, London Health Sciences Centre, London, Ontario

Correspondence: Dr Paul J Marotta, Multi-Organ Transplant Program, London Health Sciences Centre, University Campus, 339 Windermere Road, London, Ontario N6A 5A5. Telephone 519-663-3406, fax 519-663-3858, e-mail Paul.Marotta@lhsc.on.ca