Leading article

Long term outcome of liver transplantation for viral hepatitis: is there a need to re-evaluate patient selection?

Until recently, a transplant unit’s success was measured by its one year recipient survival figure. Early results were poor, but transplantation has evolved during the 1980s and 1990s into a routine treatment for which one year recipient survival approaches 90%. Developments responsible for improved recipient outcome include the refinement of patient selection criteria, advances in surgery, anaesthesia and intensive care, and refinement of immunosuppressive protocols. As the results of transplantation improved, indications for transplantation expanded and contraindications were relaxed. The inevitable consequence of success has been a consistent expansion of the recipient population. Unfortunately for the potential recipient, however, has been the failure of the organ donor pool to expand at the same rate. Of course, the relative shortage of suitable organ donors need not affect the results of transplantation, but is reflected by a growing number of waiting list deaths. Though the outcome of transplanted patients still provides one important measure of a unit’s performance, it is now appropriate that the focus shifts to an examination of the fate of all potential transplant recipients. Reflecting this change of focus, the allocation of donor organs should inevitably shift towards recipients (and liver diseases) for whom superior patient and graft outcome are predicted. Thus, graft longevity assumes increasing importance as graft loss and the need for regrafting aggravate waiting list pressure. Appropriate rationing of all resources, including the donor organ, must ensure maximum benefit for the greatest number of patients. In forthcoming years, and reflecting all constraints, it may become unacceptable to nominate high risk or high cost recipients. For many transplant programmes, these constraints are a reality, and already are reflected in waiting list management.

Thus, for each liver disease, the long term outcome of transplantation must be examined. Can transplantation be undertaken with good prospects for patient and graft survival, and with acceptable consumption of resources? The impact of disease recurrence on graft survival will become a critical issue. In this changing climate, is chronic viral hepatitis an appropriate indication for transplantation, and to what extent have recent developments affected the candidacy of these patients?

Early experience of liver transplantation for hepatitis B virus (HBV) infection highlighted the significant adverse impact of reinfection on graft and patient survival. Reflecting the effects of immunosuppression on viral replication and disease pathogenesis, aggressive graft infection with rapid progression to cirrhosis was frequently observed. In addition, subacute graft failure was experienced by some patients during the first post-transplant year. Under this circumstance, retransplantation was almost invariably complicated by more aggressive infection with accelerated loss of the second (and subsequent) graft. Though reinfection was compatible with long term survival for many, the overall outcome of transplantation for HBV infection was clearly inferior to the results of transplantation for indications such as cholestatic liver diseases. Subsequently, passive immune prophylaxis with high titre anti-HBV human immunoglobulin (HBIg) was used to reduce the risk of graft reinfection. Typical protocols required repeated and indefinite administration of HBIg from the time of transplantation. Treatment was expensive, costing as much as £10 000 ($16 000) during the first post-transplant year, and a little less per annum during subsequent years. Successful HBIg prophylaxis could achieve sustained serum negativity for viral antigens and prevention of graft hepatitis. Unfortunately, failure of prophylaxis was experienced by many patients, and was predicted by high serum viral titres at the time of transplantation. Pending the development of more effective strategies, many (probably most) transplant units concluded that patients with liver failure and high serum titres were unsuitable candidates for liver transplantation. They could, however, participate in clinical trials that were designed to assess the role of nucleoside analogues for prophylaxis in the transplant setting. Preliminary work confirmed that lamivudine prophylaxis, without HBIg, could prevent graft reinfection for the majority of treated patients. Unfortunately, failure of prophylaxis was observed for some, and was associated with the emergence following transplantation of lamivudine resistant HBV species. In ironically, it appeared that emergence of resistant virus with failure of prophylaxis was predicted by high (pretreatment) serum HBV titre. Thus, the patient with high serum HBV titre remained the Achilles’ heel of strategies utilising either HBIg or lamivudine. Consequently, many units are now assessing the combination of HBIg and lamivudine. Published results are promising, though longer patient follow up is required. It is my opinion that this combination represents the first of many strategies that have the potential to prevent graft reinfection for all recipients (irrespective of serum titre at the time of patient assessment). It seems likely that lamivudine, and/or HBIg, will be used with other antivirals that are currently under development. Safety, efficacy, and patient tolerability must be proved. Cost will be an important issue, and may determine that strategies without HBIg are preferable. Reports of late relapse following cessation of HBIg have shown that there is no justification for withdrawal of successful prophylaxis. Therefore, current and emerging strategies have the potential to achieve...
prolonged patient and graft survival, but the cumulative cost of indefinite antiviral prophylaxis will be high.

11 Recently at the American Association for the Study of Liver Diseases (AASLD) annual meeting in Chicago, a paper was presented that achieved front page billing in the national newspapers.12 The paper was newsworthy because it predicted the effects of the hepatitis C virus (HCV) epidemic on consumption of health care resources in the USA in forthcoming years. It predicted that the incidence of HCV associated liver failure would increase to equal or overtake the incidence of organ donation, thus aggravating the existing shortfall of donor livers. In that country, and in European countries other than the UK, HCV infection is already the most common indication for liver transplantation. In the UK, where the prevalence of HCV infection is somewhat lower, retransplantation is somewhat less common, but the increasing number of patients is being referred with HCV associated liver failure. Reinfecion of the graft is inevitable. Acute, then chronic hepatitis is established in the graft. Frequently, hepatitis is mild and there may be little graft damage despite prolonged infection. Subacute failure, similar to that observed for recurrent HBV infection, is occasionally observed.13 Chronic hepatitis may be aggressive, and accelerated fibrosis may cause rapid progression to cirrhosis. It has been suggested that infection with HCV genotype 1 may be associated with more aggressive graft hepatitis,14 though this claim has been disputed.15 The putative association of genotype with transplant outcome would have had no apparent implication, and patient management as this is the most common genotype, and many genotype 1 patients have a favourable post-transplant course. Despite recurrent infection, published results of transplantation for HCV suggest that the short and intermediate term (up to five years follow up) outcome is good, and not significantly different from the results of transplantation for other liver diseases.16 It seems likely, however, that the real impact of graft reinfection has been underestimated by these studies with limited follow up, and that longer follow up will show a significant incidence of graft loss as a result of recurrent disease.

The results of antiviral therapy, prophylaxis, or treatment, have been disappointing. Combination (interferon plus ribavirin) treatment of established graft hepatitis can improve chemistry and histology, and can achieve serum virus negativity during treatment for some patients.17 However, reports of sustained viral clearance following treatment of finite duration are lacking. Safety and tolerability of interferon and/or ribavirin following transplantation are not clearly established, so treatment cannot be recommended. At present, long term outcome with outcomes with no apparent complications, and existing antiviral strategies will not improve graft survival.18 Retransplantation for recurrent HCV infection has been reported.19 The reported series was small, and the results were poor, reflecting the agonal condition of some of the cohort at the time of regrafting. It seems likely that adequate patient and regraft survival could be achieved if regrafting were undertaken at an opportune time. Therefore, during the next decade, we may see waiting lists swell further with patients with graft failure resulting from HCV reinfection. How will liver units respond to the potential issue of some regraft recipients with that of the patient who is recycling for a second, or third graft? Fair play might determine that regrafting will not be an option. The situation looks dire, and can be resolved only by a massive expansion of resources, including donor livers. Meanwhile, our approach to the patient with advancing HCV infection should acknowledge these gloomy predictions. It should be remembered that established compensated cirrhosis has a remarkably good five and 10 year survival,20 superior to the results of transplantation for decompensated liver disease. Symptoms, rather than those of liver failure, are not an adequate indication for liver transplantation. Portal hypertension, bleeding, uncontrolled by liver failure, should be treated conservatively. When liver failure and/or carcinoma supervene, transplantation is indicated. At that time, recipients should be advised that reinfection is inevitable and that the consequences, for graft and patients, are unpredictable. I have attempted to summarise the recent advances in our understanding of transplantation for chronic viral hepatitis. The problem of HBV reinfection may be solved (finances permitting), but the incidence of HCV associated liver failure is probably declining. Liver failure due to HCV infection will dominate liver transplantation during the next decades. Recent developments in antiviral therapy (for the non-immunosuppressed) might retard or prevent the progression to liver failure for some patients.21 Appropriate management of complications of cirrhosis can delay the need for transplantation. Strategies for the prevention and treatment of graft reinfection are required urgently, but must be safe and well tolerated. Policies for organ allocation should be transparent, and patients need to understand the constraints imposed by resource shortage, particularly the shortfall of donor livers.

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