



Liver transplants: great advances but still great need

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Pharmaceutical background

Liver transplantation was developed in the US during the mid-1950s with initial animal experimentation. Cyclosporin was discovered as a natural fungal by-product by Jean-Francois Borel in 1972. Roy Calne then demonstrated that cyclosporin not only improved graft survival in animals, but also could cause nephrotoxicity. Further studies helped to develop safe combination regimens limiting side effects of immunosuppressive drugs by using a cocktail approach. Cyclosporin has been replaced in recent years by tacrolimus whilst mycophenolate mofetil has largely replaced azathioprine. Monoclonal antibodies can be given either at induction or the initial post-operative period as part of a calcineurin inhibitor-sparing regimen in patients with established chronic kidney

disease. By and large, the liver is a relatively immunotolerant organ and does not require large amounts of immunosuppression.

Increasing the pool of liver donors ABO incompatible donors

The organ shortage continues. The number of people awaiting organ transplantation greatly exceeds the number of organs available. The criteria for donor livers have been relaxed slightly to include non-heart-beating donors, due to the pressure for donor organs. There is increasing evidence that patients with fulminant hepatic failure can receive a donor liver, not matched to their blood group, without significant complication. ABO incompatible grafts are often used when the clinical situation requires urgent transplantation.

Living related donors and auxiliary partial transplants

A significant minority of patients can be treated by splitting the donor liver into right and left lobe and performing a partial liver transplant using one half. The quality of the donor liver and the clinical condition of the recipient are vital determinants of the risk associated with partial transplantation. The long-term benefits are a life without immunosuppression once the native liver has recovered.

Living related liver donation uses the left half of the liver, donated by a family member, often from a parent to a child, due to the lower morbidity of left lobe resections. It is also the smaller of the two lobes and a suitable size for most children.

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Indications for liver transplantation in patients with acute liver failure

Patients with acute liver failure develop multi-organ and metabolic failure; the degree to which this extends affects the outcome. King's College Hospital London, UK, was the first centre to devise a system of early indices of prognosis in patients with acute liver failure who may require liver transplantation.

Introduction

There are around 400 cases of acute liver failure (ALF) in the UK annually [1]. It is a multi-system disorder, which occurs after an acute insult to the liver leading to the development of coagulopathy and encephalopathy over a short period of time, in a patient who has no preceding liver disease. The severity is determined by the underlying aetiology, patient's age and duration of time over which the disease evolves. ALF can be classified as hyperacute, acute and subacute, which relates to the time course of the disease, within 7 days, 8–28 days and more than 28 days respectively describ-

ing the period of symptoms to onset of encephalopathy. In Denmark, the UK and the US, the commonest cause is paracetamol hepatotoxicity. In other countries hepatitis B, serologically-negative and drug-induced hepatitis are the commonest causes. 'Ecstasy'-induced hepatotoxicity is increasingly encountered in young patients. Mortality for ALF exceeded 80% until orthotopic ('in the normal position') liver transplantation became available, and is mostly related to the complication of cerebral oedema or progressive multiple organ failure and vasopressor-resistant shock in association with sepsis [2].

Diagnosis and prognosis

Spontaneous recovery in ALF ranges between 10–90% and is largely determined by the underlying pathology. Diagnosis of the underlying aetiology is consequently both important for prognosis and management. A number of blood investigations can be performed to detect hepatocellular loss and dysfunction of both hepatic metabolism and synthesis. These include aspartate and alanine transaminases, bilirubin, prothrombin time, lactate and blood glucose indicating hypoglycaemia. Specific liver disease may be suggested by specific patterns of liver dysfunction – elevated