The changing face of liver transplantation

It is now 24 years since the first orthotopic liver transplant was carried out in the United Kingdom by Sir Roy Calne in 1968. Much has occurred in the intervening years, not only in practical surgical terms but also as a result of a better understanding of the many facets of transplantation, including selection of patients, timing of the procedure, anaesthetic and other support, improved organ preservation and better management of some of the complications of the procedure. Graft rejection and sepsis are still the major causes of morbidity and mortality reflecting the difficulties in balancing immunosuppression with the inherent risks of infective complications.

Indications for transplantation are changing, particularly with respect to alcoholic liver disease, malignant liver disease and viral hepatitis. In spite of the technical advances made in recent years, increasing demand as indications for transplantation expand only serves to highlight the problem of organ shortage.

In this leading article, we review the impact of new immunosuppressive therapies, the changing indications for liver transplantation and highlight attempts to overcome the problems of donor organ shortage.

Immunosuppression

The remarkable recent improved outcome after orthotopic liver transplantation has been attributed, in part, to the development of cyclosporin A as an immunosuppressive reagent. One year survival rates after orthotopic liver transplantation are now in excess of 70%. Nevertheless caution must be used in attributing improved survival solely to one factor. Data from the European Transplant Registry show that even in the 'cyclosporin era', the proportion of patients surviving through that 12 months was increasing each year. Many of the problems of using cyclosporin have been overcome but there are still a number of well recognised side effects, in particular, nephrotoxicity which occurs in up to 90% of liver transplant recipients and may be progressive. Alternative immunosuppressive therapy to prevent, reverse or reduce other unwanted side effects have been tried, including combination with corticosteroids or azathioprine. The optimum immunosuppressive regime has not yet been defined: different centres using single, double, triple or even quadruple drug regimes. There is a remarkable lack of controlled data for assessing the optimum regime of immunosuppression.

FK506

FK506 is a new immunosuppressive agent undergoing clinical studies in organ transplantation and the management of other immune mediated diseases. Like cyclosporin A, FK506 is a fungal extract and although structurally distinct, possesses somewhat similar immunosuppressive properties. The drugs bind to different proteins both of which have cis-trans peptidyl-prolyl isomerase properties. Recent in vitro studies indicate that FK506 acts specifically by inhibiting the translation of early activation genes encoding IL2, IL3, IL4, and gamma interferon. FK506 suppresses cell mediated and humoral immune responses and prolongs survival of organ grafts in animal species. FK506 may reverse acute early chronic liver rejection. On a gram for gram basis, FK506 is between 10 and 100-fold times more potent than cyclosporin. The clinical use of FK506 has been pioneered in Pittsburgh and preliminary results are encouraging. Among 120 recipients receiving primary liver grafts, patient survival was 93% two to eight months after transplantation compared with survival in historical controls of 87%. Regrafting rates were significantly reduced in those receiving FK506. The use of additional immunosuppressive therapy for treatment of rejection episodes was reduced and nephrotoxicity was not a significant problem. Prospective, randomised studies currently underway in North America and Europe are awaited, however.

Preliminary experience with FK506 does suggest that it is associated with a number of problems: the dose is not yet firmly established; the measurement of the agent in blood is not easy, and side effects do occur, in particular neurotoxicity, diabetes mellitus, and nephrotoxicity. Studies in animals have shown that FK506 is associated with possibly fatal vasculitis but whether these results can be extrapolated to man is, as yet, uncertain.

Other immunosuppressive agents

In addition to FK506, a number of new agents with potential value in transplantation have been evaluated. Rapamycin, another fungal derivative, shows structural similarities to FK506 but has some different immune modulating properties in that IL-2 production is not blocked, but the T-cell responses to IL-2 and other cytokines are inhibited. In combination with FK506, rapamycin produces synergistic immunosuppression in mouse recipients of heart allografts and, when used alone, can prolong allograft survival and prevent allograft rejection in a number of laboratory animals such as mice, rats, pigs, and dogs. Toxicity appears to be species dependent.

RS-61443 is a morpholine ethyl derivative of mycophenolic acid. This agent, which inhibits the synthesis of lymphocyte guanosine monophosphate, has a broad spectrum of immunosuppressive action, blocking the generation of cytotoxic T-cells and suppressing B-cell memory responses. Absorption in animals is good and animal studies of renal and heart allografts suggest RS-61443 is an effective agent which induces immunosuppression with no increased susceptibility to bacterial or viral infections.

Another bacterial metabolite, 15-deoxyspergualin, has immunosuppressive properties particularly on antibody production and delayed type hypersensitivity. It is effective in animal models of rejection and has proved effective in one case of renal allograft rejection, and in reversing steroid and OKT3 resistant liver allograft rejection in man.

Prostaglandins have immunosuppressive properties in vitro, including suppression of IL-2 production and generation of cytotoxic T-cells. While there is some evidence that prostaglandin analogues may be of some benefit in renal transplantation, our own data (unpublished) suggest they have little effect in liver grafting.
MONOCLONAL ANTIBODIES
Antibodies directed against the lymphoid cells of the immune system have been important adjuncts to anti rejection therapy. Anti lymphocyte globulin has been effective in the prevention and treatment of rejection, and the monoclonal antibody OKT3 (antibody to the CD3 receptor) is very effective, not only in reversal of acute rejection but in the prevention of rejection.20 The use of OKT3 is not only not increased susceptibility to infection but also the possibility of an increased risk of lymphoproliferative disorders.21

A number of different antibodies are being developed and evaluated in animals and man. Antibodies to CD4 cells are claimed to be effective in preventing renal graft rejection.22 A chimeric antibody to CD7, an antigen present on activated T-cells, has been used to prevent renal allograft rejection but results are not yet available from long term studies. Antibodies to tumour necrosis factor, a cytokine that is both chemoattractant and cytotoxic, are also of potential value.23 Attempts to interfere with cell to cell interaction using antibodies to intercellular adhesion molecule-1 (ICAM-1) and to integrin/lFA-1 (leucocyte functional antigen-1) are of interest but await full clinical evaluation.24,25

An alternative approach uses antibodies to the IL-2 receptor. IL-2 is a growth and differentiation factor secreted by antigen-stimulated CD4+ lymphocytes, stimulating proliferation of CD4+ and CD8+ cells. The receptor is expressed on activated T-cells. Antibodies to the 55KD unit of the high affinity receptor show possible benefit in the clinical situation.26,27

Although current immunosuppression is based on cyclosporin, corticosteroids, and azathioprine, there is little agreement about optimal protocols and the benefits of single, double, or triple therapy. The next decade is likely to see the introduction of a wide spectrum of new agents with specific actions and possibly fewer side effects. The introduction of new antibodies affecting various aspects of the immune response are likely to change clinical practice. New approaches also allow greater use of xenografts but not yet for routine use in man.

Changing indications

HEPATITIS B (HBV)
Hepatitis B remains a cause of end stage liver disease world wide. Liver transplantation for hepatitis B, however, is associated with recurrence of the disease in the graft. There is a wide spectrum of reinfection: some patients may run a rapid course to cirrhosis within several months after transplantation, in others, reinfection is a serological and histological observation rather than one of clinical involvement. A unique histological pattern of disease termed fibrosing cholestatic hepatitis has recently been described in patients transplanted for chronic hepatitis B virus infection, perhaps mediated by the high cytoplasmic expression of viral antigens.28

The problem of hepatitis B virus reinfection has encouraged some centres to identify strategies to protect the graft from reinfection; these include the use of alpha-interferon (either pre- or post-transplantation),29 hepatitis B vaccine30 and passive prophylaxis with hepatitis B hyperimmune globulin.31,32 These recent approaches have evaluated therapeutic intervention regimes. Todo et al.33 treated 51 patients with end stage chronic hepatitis B virus liver disease and eight patients with hepatitis B virus related fulminant hepatic failure with orthotopic liver transplantation. Treatment of the hepatitis B virus infection was attempted with either hepatitis B virus hyperimmune globulin, combined passive prophylaxis and hepatitis B vaccine or gamma-interferon. The clinical outcome was not influenced by any of these therapies. Of the 45 patients surviving over 60 days, almost half remained HBSAg positive and in these, the pace of hepatitis redevelopment was accelerated.

Müller et al took a somewhat different approach34 and described 23 HBsAg positive transplant recipients given polyclonal hepatitis B immunoglobulin during the anhepatic phase and daily for the first eight days after transplantation. The preoperative hepatitis B virus marker profile is crucial for the recurrence rate in that those who were hepatitis B virus DNA negative (with or without HBc antibody) the recurrence rate was only 25% to 30%. In a comparative series of 110 patients receiving a similar regime of immunoglobulin among those with hepatitis B associated cirrhosis nearly half were positive for HBsAg after transplantation.35 Again, the preoperative hepatitis B virus status affects recurrence rates as those patients who were hepatitis B virus DNA positive before transplantation had an actuarial rate of hepatitis B virus recurrence at one and two years of 71 and 96% compared with a 29% one and two year recurrence rate in those who were hepatitis B virus DNA negative. Recurrence of hepatitis B in serum was associated with graft damage in that, of those biopsied, just under half the patients had chronic hepatitis and 14% had cirrhosis. A similar number of patients developed fulminant liver failure. The role of interferon and other antiviral agents such as ribavirin or ara-AMP needs to be clarified.

From these studies it seems that the hepatitis B virus DNA status of the patient is important in determining the likelihood of disease recurrence after transplantation for hepatitis B virus related liver disease. A case can be made not to transplant hepatitis B virus DNA positive patients and to treat the hepatitis B virus DNA negative patients with hyperimmune globulin, bearing in mind that this treatment may be life long. The cost of hepatitis B hyperimmune globulin is high and clearly further work is required to develop new strategies to reduce the risks of recurrent disease. It is perhaps only in the context of prospective studies that hepatitis B positive patients should be grafted.

HEPATITIS C (HCV)
With the development of more specific serological tests for hepatitis C virus it is now clear that early reinfection with hepatitis C virus commonly occurs after transplantation for chronic liver disease with positive hepatitis C virus serology.36 This reinfection usually induces rather mild inflammation, although occasionally patients may develop rapidly progressive severe viral hepatitis involving cirrhosis requiring further grafting.41 In general, hepatitis C virus infection and reinfection have a similar course.37 Anecdotal reports suggest therapy with interferon may alter the natural history but results from longer term studies are required. Contrary to earlier fears, interferon does not increase the risk of rejection.

ALCOHOLIC LIVER DISEASE
Transplantation for alcoholic liver disease continues to evoke controversy. In the early days such patients were deemed unsuitable because of concerns that such patients would return to their previous drinking habits and consequently show poor compliance with postoperative follow up and immunosuppression.38 It seems, however, that these initial prejudices were ill conceived. Results from North America and Europe have shown that survival in alcoholic liver disease can be similar to those found in other recipients with only one in 10 patients returning to their previous drinking habits.39,40 A recent study from the Mayo Clinic, however, has suggested that those transplanted for alcoholic liver disease even after
very careful selection, have a worse survival, less good quality of life and greater hospital costs.\textsuperscript{46}

Careful evaluation and screening for evidence of alcohol related damage to extra hepatic organs is paramount. The need for a period of alcohol abstinence is uncertain. In the Addenbrooke’s and King’s College Hospital series,\textsuperscript{33} patients who were drinking prior to grafting continued excessive alcohol drinking after transplantation. Studies based on a telephone survey, from the Pittsburgh group\textsuperscript{47} have shown that, in individuals who stop drinking for less than six months before transplantation, 43\% return to alcohol compared with a relapse rate of 6-7\% for individuals who stopped drinking for more than six months before surgery. Many centres now stipulate a six month alcohol free period before consideration of transplantation for end stage disease although this is controversial as alcohol abstinence may be associated with a significant improvement of liver function and survival.\textsuperscript{48}

Vaillant\textsuperscript{49} has shown that the duration of abstinence may be a poor prognostic factor for future abstinence and Starzi has claimed that death may be the price of proving abstinence. In our view the optimal approach must be to evaluate patients and their social circumstances carefully, not only by the physicians and surgeons involved but also by those experienced in alcohol counselling. The combined surgical/medical/psychiatric approach proposed by the University of Michigan\textsuperscript{50} seems to be the way forward.

The role of transplantation in acute alcoholic hepatitis is uncertain. There is not usually time to undertake full psychological assessments of patients before the therapeutic window closes and there are also no clear guidelines or series from which conclusions about timing and selection can be drawn. Clearly it is impossible for such patients to have a long period of alcohol abstinence and it is not known whether such patients will return to drinking after transplantation. In our limited experience, carefully selected patients do extremely well and there is no doubt that this form of treatment will be used cautiously but increasingly in the future.

Excessive alcohol consumption is the most frequent cause of severe parenchymal liver disease in the United States and Europe. The success of transplantation for end stage chronic alcoholic liver disease and acute alcoholic hepatitis serves to highlight the problems of donor organ shortages.

**Organ donation**

The increasing availability of liver transplantation, highlights the shortage of organ donors. According to the United Kingdom transplant service (personal communication), in the first six months of 1991 10 patients died on the emergency liver transplant list before a suitable liver could be found (41 emergency patients were successfully transplanted during this time). Two recent studies have highlighted these shortages and, in particular, have emphasised the possibility of increasing donor supplies\textsuperscript{55-56}. Suggested methods include altering the management of patients aged between the 50–60 years dying of severe cerebrovascular disease in general hospitals, by increasing the proportion of those ventilated, reducing the refusal rates of relatives, avoiding the non-procurement of suitable organs and preventing the deterioration of initially suitable organs, converting restricted offers to unrestricted offers and ensuring discussion with families. While these suggestions raise a number of potential ethical problems, this approach could increase the number of organ donors.

Until organ supply can be improved, surgeons have looked for approaches to use livers more effectively.\textsuperscript{57} These include the use of split livers (whereby one liver is given to two recipients) and reduced sized livers. These techniques are of particular help in children where organ donations and organ size are a greater problem. Broelsch et al\textsuperscript{58} in a series of 25 split liver transplants performed over a 3-5 year period report survival figures of 67\% patient and 55\% primary graft survival in 21 children (the discrepancy arising as 12\% of children were alive as a result of a further transplant) and 25\% patient and graft survival in four adults. Survival figures for full-size orthotopic transplantation were 81\% in 57 patients over the same period. Split liver grafting, however, was associated with the highest mortality and complication rates. The resources required to perform a split liver graft are enormous and the strain put on the transplant surgeons to harvest and split the liver and then perform two transplant procedures are considerable.

More recently a further technique has been applied to organ shortages, that of transplantation from living related donors (where donors undergo total left hemi hepatectomy for procurement of the graft). To date there is little published work on this controversial area, although early results from Chicago,\textsuperscript{59} where five such transplants have been performed, have shown 100\% patient and donor survival over a two to six month period. Until recently, the debate has concentrated on children receiving a liver from a live related donor for chronic liver disease, however, this has now been extended to a child with fulminant hepatic failure. One live related donor operation has so far been carried out in Europe. Ethical considerations, much debated in the medical press, still remain a major area of debate with regard to living related donors. The donor operation is long and not free of risk. The medical concept of Primum non nocere must remain paramount. In our opinion, the right way forward is to concentrate efforts on increasing organ donation and developing better tests for assessment of ‘marginal livers’ rather than expose patients relatives to additional pressures at an already highly stressed period.

Finally, the technique of auxiliary liver grafting\textsuperscript{58} deserves mentioning. This technique means possibly simpler surgery as the patient’s own liver is left in situ. This method has been used in patients with metabolic liver disease, chronic liver disease, and fulminant liver failure (usually from paracetamol poisoning). As yet no clear benefit to the patient has emerged from this technique, which in cirrhotic patients is associated with the risk of developing hepatocellular carcinoma in the patient’s own liver.\textsuperscript{60}

**Conclusions**

In this review, only certain aspects in the advances of transplantation have been discussed. We think that no patient should die from liver disease without transplantation having been considered. This may require no more than a fleeting thought on the part of the surgeon or physician responsible for that patient, but if there is any doubt, all liver transplant units are more than happy to discuss potential referrals.

The next decade will undoubtedly see the introduction of newer techniques and the greater use of techniques still in their infancy such as auxiliary transplantation, islet cell transplants, and gene therapy for correction of metabolic diseases.

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