Liver transplantation for viral hepatitis

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Viral hepatitis is associated with two forms of liver failure that may require liver transplantation: fulminant hepatic failure associated with all forms of acute viral hepatitis and chronic liver failure as a result of chronic hepatitis B and C infection (or both). This review briefly discusses liver transplantation for fulminant hepatitis but focuses on transplantation for hepatitis B- and hepatitis C-associated cirrhosis.

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Fulminant hepatic failure (FHF) may result from any form of acute viral hepatitis – hepatitis A through to hepatitis E (Williams, 1996). FHF is exceedingly rare in acute hepatitis C virus (HCV) infection but occurs in approximately 1 in 1000 cases in other forms of acute viral hepatitis. The decision to proceed to liver transplantation is dependent upon the severity of the fulminant hepatitis and the underlying cause (Bernal and Wendon, 2004). These two factors determine the natural history and chance of recovery without liver transplantation. For example, fulminant hepatitis A is much more likely to recover spontaneously than fulminant hepatitis B or hepatitis E. The likelihood of spontaneous recovery from fulminant hepatitis can be assessed using the Kings criteria (*Table 1*) (Bernal and Wendon, 2004). The presence of three of the five Kings criteria has a positive predictive value for death without liver transplantation of over 90% and liver transplantation is usually undertaken in these circumstances once such criteria are met.

The outcomes of liver transplantation for FHF are inferior to those for cirrhosis (Bernal and Wendon, 2004). Transplantation for FHF is performed in an emergency setting and although there is no underlying portal hypertension, mortality from sepsis or cerebral oedema is increased. Furthermore, because progression to cerebral oedema and multiorgan failure may be rapid, and because donor organ shortages exist in many parts of the world, it is not uncommon for a patient to die while awaiting urgent transplantation.

TABLE 1.
Kings criteria for the prediction of death without liver transplantation in fulminant hepatic failure not caused by paracetamol overdose*

Serum bilirubin > 300 μmol/litre
Onset of hepatic encephalopathy >1 week following the onset of jaundice
Prothrombin time >50 seconds
Age <10 years or >40 years
Aetiology: non A, non B hepatitis

*Three or more of the above five criteria predict death in 90% of cases without transplantation

TRANSPLANTATION FOR HEPATITIS B-ASSOCIATED CIRRHOSIS

Indications for transplantation

Liver transplantation is generally considered following the onset of hepatic decompensation. Usually, the Child Pugh score (CPS) is 8 or above (*Table 2*). Occasionally single clinical features such as ascites or encephalopathy direct decision-making. In the United States, the model for end-stage liver disease (MELD) scoring system is used to determine indications for liver transplantation and priority on the waiting list (Christensen, 2004).

Antiviral therapy pretransplant

Lamivudine therapy has significantly improved the outcomes of decompensated hepatitis B virus (HBV)-associated cirrhosis. There is now evidence of improvement in CPS and a decrease in the need for hospital admission for resistance ascites, spontaneous bacterial peritonitis and encephalopathy (Villeneuve et al, 2000; Yao et al, 2001). Improvements are seen in both hepatitis Be antigen (HBeAg) positive- and HBeAg negative-associated cirrhosis.

Lamivudine has also been shown to delay the onset of decompensation and potentially to decrease the hepatocellular cancer (HCC) risk in patients with compensated cirrhosis (Liaw et al, 2004). Lamivudine is well tolerated and is not associated with significant side effects. However, while many patients improve on lamivudine, there is a subgroup of patients who

present with rapidly progressive disease, in whom fatal outcomes are seen despite the introduction of lamivudine.

Fontana et al (2002) determined that elevated pre-treatment serum bilirubin and creatinine levels and a detectable HBV DNA (by branched chain DNA assay) were associated with early mortality, and derived a predictive model to determine the probability of death. Patients with a high predicted probability of death should be listed for liver transplantation rather than awaiting a possible beneficial effect of lamivudine therapy.

In addition to the issue of early lamivudine failure, the emergence of lamivudine resistance in patients with previous hepatic decompensation or even compensated cirrhosis may lead to a severe hepatic flare. Such a flare may result in rapid hepatic decompensation, requiring semi-urgent liver transplantation. In this situation, treatment with adefovir (10 mg daily) may be associated with a rapid decrease in HBV DNA and progressive clinical improvement. While adefovir therapy is safe and well tolerated, some patients fail to improve quickly enough to avoid liver transplantation. Increasingly, patients undergoing liver transplantation for chronic hepatitis B-associated liver failure already have lamivudine resistance, and are going to transplantation on combined lamivudine and adefovir therapy or on adefovir monotherapy.

Antiviral therapy post-liver transplantation

In the past, recurrence of hepatitis B after liver transplantation was a major problem resulting in high rates of graft loss and patient death. Hepatitis B recurrence is now uncommon following liver transplantation. Recurrence is prevented by the use of antiviral therapy in combination with hepatitis B immunoglobulin (HBIG) (*Table 3*). Antiviral therapy usually comprises lamivudine monotherapy or combination lamivudine plus adefovir if lamivudine resistance has emerged pretransplantation. HBIG is given on a daily basis early after transplant but is then decreased to weekly and later monthly, and often continued lifelong.

The most cost-efficient HBIG protocol is a source of significant controversy in the liver transplant community (Villamil, 2003). Units such as the authors' in Australia and some in New Zealand use very low dose HBIG (400–800 units intramuscularly) aiming for anti-hepatitis B surface antigen (HBsAg) titres between 50–100 units/litre. This results in a recurrence rate <5% (Angus et al, 2000). Elsewhere in the world, much higher doses of HBIG are used, up to 10 000 units intravenously on a monthly basis with targeted anti-HBs titres greater than 100 units/litre and sometimes over 250 units/litre.

Whether given intravenously or intramuscularly, HBIG therapy is inconvenient to the patient. Some transplant units attempt to stop HBIG therapy at 12 months or 2 years following liver transplantation. This seems to be possible in patients who are truly HBV DNA negative before antiviral therapy commences pretransplantation or in patients who receive HBsAg vaccination and develop their own anti-HBs titres (Sanchez-Fueyo et al, 2000; Villamil, 2003).

Transfer of anti-HBs positivity from HBV-immune donors to recipients has been observed following liver transplantation in recipients treated post-transplant with lamivudine monotherapy (Lo et al, 2003). When this occurred, presumed to be as a result of the transfer of immune donor leukocytes, anti-HBs titres were sustained for a median of 221 days (range 94–1025 days). The long-term efficacy in prevention of HBV recurrence using this approach remains to be determined.

TABLE 2.
Severity scoring systems for hepatitis B virus- or hepatitis C virus-associated cirrhosis

Child Pugh score*		**1**	**2**	**3**
Encephalopathy		None	Grade 1–2	Grade 3–4
Ascites		Absent	Slight	Moderate/marked
Bilirubin (μmol/litre)	Non-cholestatic	17–34	35–51	>51
	Cholestatic	17–68	68–168	>168
Albumin (g/litre)		>35	28–35	<28
INR		<1.7	1.7–2.3	>2.3
MELD score†				
Log_e bilirubin (mg/dl) + Log_e creatinine (mg/dl) + Log_e INR				

*a score of > 8 usually leads to listing for liver transplantation. †a MELD score of 15 usually leads to listing for liver transplantation. For MELD calculator go to: http://www.unos.org/resources/MeldPeldCalculator.asp?index=98 INR = international normalized ratio; MELD = model for end-stage liver disease

TABLE 3.
Antiviral protocols for hepatitis B virus (HBV)-associated cirrhosis requiring liver transplant

Pretransplant	Lamivudine
	Lamivudine and adefovir
Post-transplant	Lamivudine or lamivudine and adefovir
	Hepatitis B immunoglobulin (HBIG)*†

*high dose intravenous injection HBIG, aiming at titres >1:100; moderate dose intramuscular injection HBIG, aiming at titres >1:100; low dose intramuscular injection HBIG, aiming at titres >1:50; † may be ceased in patients who respond to hepatitis B surface antigen vaccination or who were HBV DNA negative pre-lamivudine therapy

Outcomes

The outcomes of liver transplantation for HBV using antiviral therapy both pre- and post-transplant are now excellent. In a recent report, 1-year survival of 87% and 5-year survival of 76% was achieved. This has dramatically changed from over a decade ago where 5-year survival rates were in the order of 50% (Kim et al, 2004).

TRANSPLANTATION FOR CHRONIC HEPATITIS C-ASSOCIATED CIRRHOSIS

Indications for liver transplantation

These are usually the same as for HBV-associated cirrhosis: hepatic decompensation with a CPS > 8.

Antiviral therapy pretransplant

Antiviral therapy with combination pegylated interferon plus ribavirin has lead to sustained virological response (SVR) rates in the order of 40% for HCV-positive cirrhosis genotype 1 and 60–70% for HCV cirrhosis genotype 2/3 (Hadziyannis et al, 2004). However, patients treated in these studies had compensated disease and generally had no clinical features of cirrhosis. Experience using such an approach in patients with clinical evidence of cirrhosis, borderline decompensation or frank decompensation is limited.

Patients with mild decompensation have been treated on transplant waiting lists in programmes offering living related liver donation. The approach has been to start at low doses of interferon and ribavirin and gradually increase the dosage as tolerated, the so-called low dose accelerating dosage regimen (Wiesner et al, 2003). In this manner, significant SVR rates can be obtained before transplantation is undertaken, particularly for genotype 2/3, with early evidence suggesting that if the virus is truly cleared recurrence does not occur. Unfortunately, the efficacy of this approach is lower for genotype 1.

TABLE 4.
Antiviral therapy in hepatitis C virus infection

Pretransplant	Only in mild decompensation (Child Pugh score < 7)
	Limited by degree of thrombocytopenia
	Commonly requires support with erythropoietin and/or GCSF
	SVR up to 50% genotype 2/3
	SVR 15% in genotype 1
Post-transplant	Early (pre-emptive) therapy results in SVR <15%
	Treatment of established hepatitis C virus recurrence results in SVR of 20%
	High drop-out rate and use of erythropoietin and/or GCSF

GCSF = granulocyte colony stimulating factor; SVR = sustained virological response

This group of patients has increased requirements for support of anaemia and neutropenia with erythropoietin and granulocyte colony-stimulating factor (GCSF). A limiting factor to treatment of patients with cirrhosis is often thrombocytopenia. A platelet count <50 000 virtually precludes therapy. There are published data on attempts to treat patients with more advanced liver disease but this has been unrewarding (Crippin et al, 2002).

Antiviral therapy post-transplant

Hepatitis C recurrence is universal in patients transplanted while viraemic for hepatitis C. Attempts have been undertaken to try to use antiviral therapy post-transplant before the onset of clinical hepatitis C recurrence, typically at about 3 months. Although this approach has significant appeal, it has been limited by the poor tolerability of HCV therapy early post-transplant, particularly with problematic neutropenia and anaemia (Garcia-Retortillo and Forns, 2004). In unpublished studies, SVR was only achieved in 8% of cases.

Most of the data relating to anti-HCV therapy have been for patients who have established chronic hepatitis C in the post-transplant period (Samuel et al, 2003; Terrault et al, 2004). Treatment is usually commenced somewhere between 12 months and 2 years post-transplant. There are several small studies now reported in this group of patients but the data are limited, particularly for combination pegylated interferon and ribavirin (Dumortier et al, 2004). In general, the SVR seems to be reduced compared with the non-transplant setting with SVR rates in the order of 20–30%. There is a high requirement for supportive erythropoietin and colony stimulating factors. Dose reduction and cessation of

TABLE 5.
Factors predicting worse outcomes for hepatitis C virus infection post liver transplant

Donor age
Pretransplant viral load
Cytomegalovirus infection
Tacrolimus therapy
OKT3 therapy
Pulses of corticosteroid therapy
Rapid tapering of corticosteroid therapy
4-month post-transplant viral load
Interleukin (IL)-2 receptor monoclonal antibody therapy

therapy are common. The results of antiviral therapy for recurrent HCV infection post-transplant remain disappointing.

Outcomes

The outcomes for patients with chronic HCV-associated cirrhosis undergoing liver transplantation are limited by the universal recurrence of the virus. Antiviral therapy to date has not had a major impact on the outcomes, although individual patients clearly have benefited when SVR is achieved. Emerging data indicate worse outcome for HCV-positive compared to HCV-negative patients following liver transplantation (69.9% *vs* 76.6% at 5-year follow up; Forman et al, 2002). This is largely the result of an increased progression to cirrhosis in the post-transplant period.

The mean time to cirrhosis is approximately 10 years compared to 20–30 years in the non-transplant setting. Factors that predict progression to cirrhosis include donor age, cytomegalovirus (CMV) infection, pretransplant viral load, and various immunosuppressive regimens (Berenguer, 2003). In particular, it seems that tacrolimus therapy, rapid tapering of corticosteroid therapy, pulse corticosteroid therapy and OKT3 therapy are all associated with worse outcomes. *Table 6* outlines the principles of immunosuppressive therapy, donor selection and CMV prophylaxis in these patients. It may be impossible to avoid some risk factors in the context of transplantation for HCV. However, the avoidance of a combination of negative factors is highly desirable and may limit the progressive nature of HCV in the post-transplant period.

WHAT ABOUT HEPATOCELLULAR CANCER?

HBV-positive cirrhosis and HCV-positive cirrhosis are commonly complicated by HCC. HCC develops in approximately 2–5% of such patients per annum and is found in between 20 and 30% of HCV- or HBV-positive patients undergoing liver transplantation for decompensated cirrhosis. In many cases, HCC itself is the indication for liver transplantation. Patients selected for liver transplantation generally satisfy the Milan criteria (*Table 7*). In such patients, recurrence of HCC is infrequent (in the order of <10%) and the outcomes of transplantation are excellent with 90% 1-year survival and 80% 5-year survival (Adam and Del Gaudio, 2003).

TABLE 6.
Clinical practice to improve outcomes for HCV post-liver transplantation

Avoid use of older donors (e.g. > 60 years) for HCV-positive recipient
Universal prophylaxis against cytomegalovirus infection
Do not use pulse corticosteroids as initial therapy for acute rejection and HCV infection
Avoid antibody therapy
Slowly taper corticosteroids

HCV = hepatitis C virus

USE OF HCV-INFECTED OR HBV-INFECTED DONORS

Use of HCV antibody-positive liver donors

It is now recognized that livers from anti-HCV positive donors can be used for HCV recipients awaiting liver transplantation (Arenas et al, 2003). There have been small series of patients where the outcomes for liver transplantation using such donors are no different to those using HCV antibody negative donors. There are limited data suggesting that if the genotype of the donor becomes predominant post-transplant, then the outcomes for the HCV infection post liver transplantation are improved.

Use of HBV core antibody-positive liver donors

Donors who have evidence of past hepatitis B infection, i.e. those who are HBV core antibody (antiHBc) positive and HBs antigen negative, often have low levels of residual HBV in the liver. Following liver transplantation, immunosuppression may lead to HBV reactivation. Indeed such donors have been shown to transfer hepatitis B infection to the liver recipient in up to 80% of cases (Lee et al, 2001). These donors, however, can be used for HBV surface antigen positive recipients. More recent data suggest that lamivudine monotherapy alone can prevent infection even when such livers are transplanted into HBsAg negative recipients.

CONCLUSIONS

Viral hepatitis, particularly chronic hepatitis B and C, with or without HCC, is a major indications for liver transplantation throughout the

TABLE 7.
Selection criteria for hepatocellular cancer patients undergoing liver transplantation

Single lesion < 5 cm
Multiple lesions < three, each < 3 cm in diameter
No metastatic disease
No vascular invasion

world. Decompensated hepatitis B cirrhosis can now be effectively controlled with antiviral therapy, often avoiding liver transplantation. HBV recurrence is prevented in over 95% of cases using current protocols. HBV core antibody donors can be safely used for HBsAg negative recipients under antiviral therapy.

HCV recurrence is currently the major challenge facing liver transplant units around the world. Antiviral therapy pretransplant and post-transplant is not significantly altering outcomes in the vast majority of patients. Thus it is important to optimize donor selection and immunosuppressive therapy and to prevent other complications in the post-transplant period. Increasingly, HCV antibody-positive donors are being matched with HCV-infected recipients, without compromising outcomes.

Finally, although HBV and HCV remain major challenges, there are now data that both diseases can be treated pretransplant, disease recurrence can be prevented or controlled with antiviral therapies and infected donors can be used. These challenges are being met in HBV disease, but the problem of HCV disease will require improved and better-tolerated antiviral therapies. **HM**

Conflict of interest: Professor McCaughan is on the scientific advisory board for Roche Transplantation (Australia) and Janssen–Cilag (Australia).

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KEY POINTS

- Liver failure as a result of chronic viral hepatitis is now the most common indication for liver transplantation around the world.
- Antiviral therapy has significantly improved the outcome of decompensated hepatitis B-associated cirrhosis. However, the development of lamivudine resistance may result in rapidly progressive hepatic failure which may require liver transplantation.
- Prophylactic regimens to prevent hepatitis B recurrence post-transplantation have resulted in excellent long-term outcomes for patients undergoing transplantation for chronic hepatitis B.
- Post-transplant recurrence of hepatitis C may result in rapidly progressive cirrhosis and early graft loss. Risk factors associated with severe hepatitis C recurrence include intensive immunosuppression, donor age, cytomegalovirus infection and pretransplant viral load.
- In patients with hepatitis C, antiviral treatment with interferon/ribavirin based-regimens is poorly tolerated both in patients with decompensated cirrhosis and in the post-transplant settings, leading to poor response rates and little impact on overall outcomes.
- Liver transplantation for hepatocellular carcinoma is indicated in patients fulfilling strict criteria. Use of the Milan criteria results in excellent long-term outcomes.
- Donors with evidence of chronic viral hepatitis may be suitable for transplantation, as long as prophylactic antiviral therapy is used.

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