Hepatitis C and liver transplantation

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Liver transplantation is a life-saving therapy to correct liver failure, portal hypertension and hepatocellular carcinoma arising from hepatitis C infection. But despite the successful use of living donors and improvements in immunosuppression and antiviral therapy, organ demand continues to outstrip supply and recurrent hepatitis C with accelerated progression to cirrhosis of the graft is a frequent cause of graft loss and the need for retransplantation. Appropriate selection of candidates and timing of transplantation, coupled with better pre- and post-transplant antiviral therapy, are needed to improve outcomes.

When antiviral therapy fails in hepatitis C virus (HCV) infection, or if diagnosis of the disease is delayed until the appearance of decompensated liver disease with portal hypertension, the only option for the individual is liver replacement. Currently, over 17,000 individuals are awaiting orthotopic liver transplantation, and fewer than 5,000 liver transplants are performed per year (for the latest data see the Organ Procurement and Transplantation Network website at http://www.optn.org/data) . This represents the greatest challenge in liver transplantation: namely, the demand for organs vastly outstrips the supply.

Hepatitis C is the most common indication for orthotopic liver transplantation, accounting for 40–50% of both individuals on the waiting list and those who have undergone liver transplants. Thus, there are insufficient donor organs even if only transplant candidates with HCV are considered. Unfortunately, liver transplantation is not a cure for hepatitis C. Viral recurrence is universal and damage to the new liver occurs routinely. Recurrent HCV infection is among the leading causes of graft loss and the need for retransplantation. Thus, the challenges in liver transplantation as a treatment for hepatitis C include accessing adequate numbers of liver grafts and controlling the virus before and after transplantation to mitigate recurrent disease.

Listing for transplantation

After evaluation, acceptable candidates for liver transplantation in the United States are registered with the United Network for Organ Sharing (UNOS). This organization runs a centralized computer network that includes the waiting list of every transplant hospital and that links all organ procurement organizations. Organs are allocated first locally in an organ procurement organization, and then regionally in the 11 UNOS areas, and finally nationwide for individuals with chronic liver disease.

Prioritization on the waiting list

Organ allocation was previously based principally on location (whether the individual was at home, in hospital or in intensive care) and on waiting time. Allocation has recently shifted to a risk-based priority system that uses MELD, a mathematical model for end-stage liver disease. MELD is based on logarithmic transformation of the potential recipient's INR (a measure of blood clotting), bilirubin and creatinine. MELD predicts short-term mortality for those on the waiting list more accurately than does the Child–Pugh score (a scoring system for severity of cirrhosis), which was previously used in the organ allocation scheme.

Within a distribution unit, individuals with the highest MELD score (which ranges from 6 to 40) have the highest priority for transplantation, and waiting time is used only to discriminate between individuals with the same MELD score. Currently, however, the MELD score of transplant recipients varies widely in the different organ procurement organizations. Donor organs should be allocated to individuals who are most likely to benefit from a transplant[1]. In the first 18 months after the MELD-based allocation system was introduced, the overall pre-transplant mortality decreased[2]. Recipient and graft survival also increased after the MELD model was implemented.

Individuals with hepatitis C are allocated organs according to their MELD scores, but they receive additional priority if they develop hepatocellular carcinoma (HCC). Additional MELD points are given to all individuals with HCC because laboratory MELD scores do not reflect the mortality risk from this disease. In the previous allocation scheme, the low priority given to these individuals led to a high

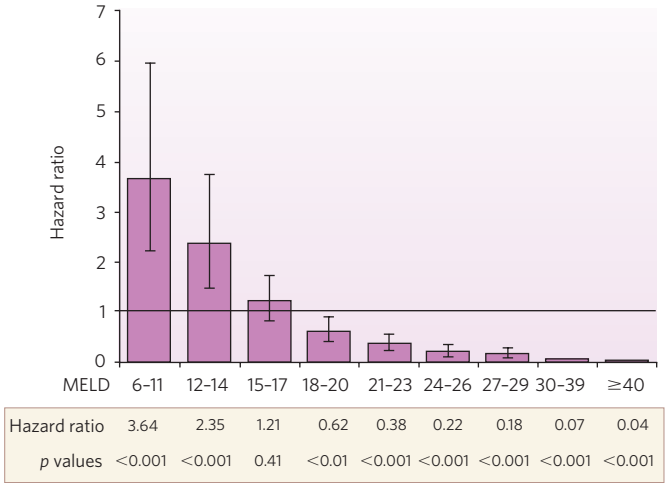

Figure 1 | The mathematical model MELD can predict the survival of candidates waiting for a liver transplant. Individuals who have MELD scores higher than 15 derive a progressively increasing survival benefit with each subsequent increment in their score[4]. The hazard ratio is defined as the likelihood of death during the year after undergoing transplantation compared with remaining on the waiting list. A hazard ratio of more than 1 means that a patient is more likely to die with transplantation and a ratio of less than 1 means the patient is less likely to die with transplantation.

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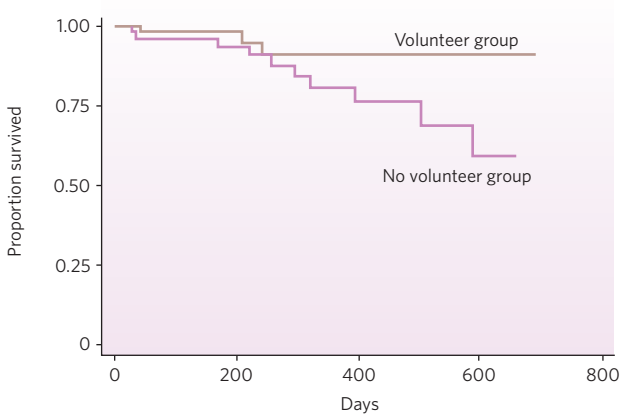

Figure 2 | Survival benefit of pursuing live donor liver transplantation (LDLT). Monitoring the survival of candidates on the transplant waiting list with (volunteer group) and without (no volunteer group) a potential donor shows the benefit of LDLT[10].

dropout rate caused by tumour progression. Because individuals with HCC benefit from early transplantation before metastasis or growth of the lesion, those with small tumours (fewer than three lesions < 3 cm or one lesion < 5 cm) are given added priority: they start with a minimum MELD score of 22 and their score is increased every 3 months. No priority is given to those with tumours that exceed these size limits owing to the increased risk of recurrent HCC after transplantation. This change in allocation has resulted in a marked increase in the proportion of individuals with HCC receiving a transplant, and has decreased both the waiting time and the dropout rate. The availability of accelerated transplantation has increased the value of screening for HCC in individuals with HCV-related cirrhosis.

Timing of transplantation

Owing to regional variances in the criteria for placing an individual on the waiting list for liver transplantation, in 1997 the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases published recommendations regarding the minimum criteria that an adult should meet to be put on this list[3]. These guidelines recommend that an individual placed on the waiting list should be ready to proceed with transplantation immediately should an organ become available. To qualify for listing, the individual's expected chance of surviving 1 year without transplantation should be 90% or less. On the basis of published data, individuals with a Child–Pugh score of seven or more, or those with bleeding associated with portal hypertension, meet these criteria and should be evaluated and listed for transplantation.

The timing of transplantation involves determining when an individual will derive the maximum benefit from receiving a new liver. The goal is to avoid both premature transplants when liver disease is not advanced and futile transplants when individuals are too sick. On the one hand, if the transplant is performed before liver failure develops, then the morbidity and mortality of the transplant operation will outweigh the benefits. This is particularly true for hepatitis C, for which delaying the initiation of recurrent HCV in the new graft may add years to an individual's life and may allow time for the development of a new antiviral therapy. Thus, early transplantation is potentially more harmful for these individuals, unless it is linked to pre-transplant antiviral therapy and HCV eradication (see below). On the other hand, if a transplant candidate is moribund, then the surgical risks of the procedure can become prohibitive.

A recent study[4] suggests that those with MELD scores of less than 15, particularly less than 12, do not derive a survival benefit in the first year, whereas the survival benefit increases with each increment in score for those with MELD scores of more than 15 (Fig. 1). At high MELD scores (>30), the risk of dying after transplantation was found to increase by 50% and more individuals were removed from the waiting list for the reason of 'death' or 'too sick', but outcomes in the sickest individuals were still reasonable, especially given the over 300-fold increase in pre-transplant mortality in candidates with high MELD scores[4]. Other studies indicate that the MELD score is a relatively poor predictor of post-transplant outcomes in all but individuals with the highest 20% of MELD scores[5].

However, retransplant candidates, individuals with renal failure requiring dialysis and those requiring mechanical ventilation, particularly older individuals, have a significantly increased risk of operative mortality[5]. The presence of two or more risk factors predicts a very low post-transplant survival. Similarly, in living donor transplant recipients, analysis of UNOS data has shown that being in the intensive care unit before transplant, retransplantation, female donor to male recipient transplantation, being 44 yr or older and of non-white recipient race can increase the rate of retransplantation, but not death[6]. Thus, there is no absolute cut-off in MELD score for transplantation futility.

Thus, the optimal time for liver transplantation is when an individual achieves a MELD score of 15 or more or begins to show evidence of decompensation, manifested by synthetic dysfunction, or malnutrition. Although prioritization for orthotopic liver transplantation is not affected by an early referral, it does allow pre-transplant problems to be addressed and the management and timing of transplantation to be optimized.

If an individual would not derive a survival benefit from transplantation—either because their condition has worsened such that the procedure's risks outweigh its benefits or, rarely, because the individual's condition has improved—it is appropriate to remove them from the list permanently or temporarily.

Living donor liver transplantation and hepatitis C

First performed in children in 1989 (ref. 7), living donor liver transplantation (LDLT) has been performed from adult to adult in the United States since 1998 (ref. 8). Because living donation permits transplantation to take place independent of either waiting time or the severity of liver disease, the criteria required for LDLT differ from those required for deceased donor liver transplantation (DDLT). Because a living donor organ has significantly less cold ischaemia time than does a deceased donor organ because it is transferred immediately from donor to recipient, and because it is from a healthy, extensively screened individual, living donor livers are potentially of better quality than are deceased donor livers. The living donor allograft, however, has significantly less hepatic mass than has a full-sized deceased donor organ. So far, the outcomes of living donation and deceased donor transplantation have been similar.

The reduced waiting period for a living donor organ — the principal benefit of living donor transplants — may decrease the risks of decompensation or death before transplantation, thereby improving the overall chances for success. Data show that individuals on the waiting list with potential donors for LDLT have improved survival: their mortality is half that of those listed only for DDLT[9,10] (Fig. 2). Because the transplant is done on an elective basis, the operation can proceed immediately after the workup. Alternatively, the flexibility of the waiting period before transplantation in living donor recipients can allow an attempt at pre-transplant viral eradication. It seems that if the recipient is negative for serum HCV RNA on therapy, then LDLT leads to a very low percentage (10%) of post-transplant viral recurrence[11]. This can facilitate a cure for hepatitis C through transplantation — an important issue because over half the individuals on the waiting list who have been previously treated cannot tolerate a full course of therapy or relapse (see below). Thus, viral eradication may be an indication for earlier transplantation by LDLT in individuals with HCV at a stage when they can tolerate antiviral therapy.

LDLT grafts have tremendous growth potential: the graft generates over 150,000 hepatocytes every second in the first week after transplantation and doubles in size within 4 weeks[12,13]. Concerns have been raised about the effect of accelerated growth that follows LDLT grafts. Theoretically, this growth potential may predispose individuals trans-

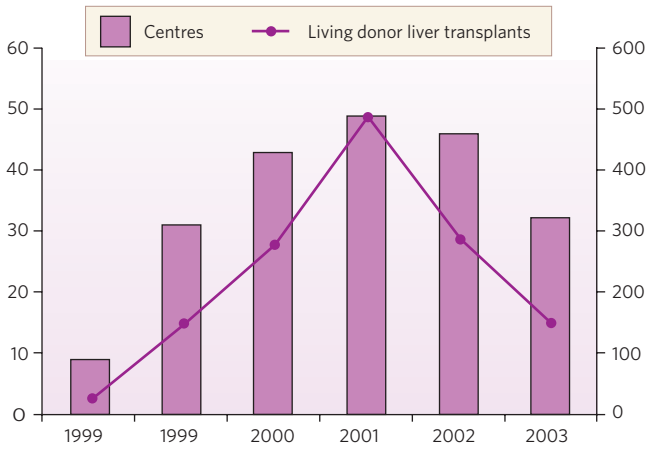

Figure 3 | Number of live donor liver transplants in the United States. Shown are the number of centres performing LDLT and the number of adult LDLT operations performed from 1998 to 2003 in the United States[21].

planted for HCV cirrhosis to a more aggressive recurrence of HCV. Two large studies have shown that the incidence and severity of HCV recurrence do not differ between DDLT and LDLT recipients[14,15]; however, another study has found that the incidence of cholestatic hepatitis, a particularly virulent and rapidly destructive form of recurrent HCV, is significantly greater in LDLT recipients[16]. Recently, a careful comparison of protocol liver biopsies from 23 LDLT and 53 DDLT recipients found no significant differences in the degree of hepatic inflammation between the two groups over 3 years, and similar or less fibrosis in the LDLT group, which reached a plateau after 12 months[15].

Individuals with decompensated cirrhosis who meet the standard indications for orthotopic liver transplantation do not have any contraindications and have MELD scores of 15 or higher are the most appropriate candidates for LDLT. A simple rule is that an appropriate LDLT candidate is one who would undergo transplantation immediately if organs were unlimited. MELD can help to identify individuals who are not likely to benefit from LDLT because they are either too sick or too well to undergo transplantation[17]; however, the number of potential LDLT operations is limited. In one centre, 51 out of 100 individuals evaluated for LDLT were rejected[18]. The most frequent reasons for rejection included medical co-morbidity, high-risk psychosocial issues, obesity, financial issues and the procurement of a deceased donor organ during the evaluation[18]. Overall, in experienced centres about a third of adults on the waiting list may have a potential donor and half of these will undergo the procedure; thus, LDLT may be applicable in up to 15% of individuals on the list[19]. Between 2001 and 2003, however, the number of centres performing the procedure and the number of LDLT cases dropped markedly[8,20,21], and currently less than 5% of all adult liver transplants use living donors (Fig. 3). This reluctance to perform LDLT may be related to two highly publicized donor deaths[20,21]. With increased experience and the lessons learned from A2ALL, a living donor cohort study funded by the NIH, it is hoped that living donation will expand to meet organ demand better in the future.

Predictors of hepatitis C after liver transplantation

Recurrent HCV remains a persistent problem and a leading cause of graft loss. In individuals who have active HCV replication before transplantation, the reacquisition of viraemia after transplantation is universal. Attempts to prevent reinfection with immune globulin or other agents have not been successful[22]. Reinfection occurs during reperfusion of the liver allograft, and viral titres reach pre-transplant values at about 72 h (ref. 23). At steady state, the HCV viral load is, in general, ten times higher after transplantation than before. Histological recurrence with allograft hepatitis owing to HCV occurs in up to 90% of individuals by the fifth year after transplantation[24].

Although histological injury in the allograft owing to HCV is exceedingly common, progression of hepatitis C is variable: some individuals experience indolent disease, whereas others progress rapidly to cirrhosis and liver failure. In those that develop recurrent cirrhosis after transplantation, rapid decompensation is common. Up to 42% of individuals with HCV-related cirrhosis after transplantation have been reported to develop decompensation, manifested as ascites, encephalopathy or hepatic hydrothorax, and less than 50% of individuals survive for 1 year after they develop decompensation[25]. Thus, data indicate that the progression of hepatitis C is accelerated after orthotopic liver transplantation as compared with non-transplanted individuals.

Several factors have been associated with the increased severity of recurrent HCV and the decreased recipient survival. For example, although grafts from donors over 60 years (up to 80 years) function without a negative impact on recipient outcomes[26,27] in individuals without HCV, the use of these grafts in HCV-positive recipients requires caution. Data suggest that there may be a more severe recurrence of HCV and a more rapid progression to cirrhosis when older donors are used[28]. No adverse outcome has been found, however, when selected HCV-positive grafts with no significant liver disease are used[29–31] or when grafts positive for hepatitis B core antibody but negative for surface antigen are used[30].

Of recipient factors, higher HCV viral loads before transplantation correlate with lower recipient survival after transplantation. For example, individuals with an HCV RNA titre of more than 1×10^6 copies per ml before transplantation were found to have a cumulative 5-year survival of 57% as compared with 84% for those with HCV RNA titres of less than 1×10^6 copies per ml (ref. 32). It is not known, however, whether reducing viral load will improve these outcomes. Research is currently focused on developing antiviral strategies to reduce or to eliminate the pre-transplant viral burden to lessen post-transplant recurrence. In addition, advanced recipient age, hyperbilirubinaemia, increased INR and pre-transplant cytomegalovirus status adversely affect survival after transplantation[33]. Whether factors such as obesity or alcohol use accelerate histological progression after transplantation has not been well studied, but their effects are likely to be similar to those in the non-transplant setting.

Immunosuppression and HCV recurrence

Because hepatitis C progresses more rapidly after transplantation, the choice and extent of immunosuppression have been an area of active research and controversy. Standard post-transplant immunosuppression consists of a calcineurin inhibitor (tacrolimus or cyclosporine) and a tapering dose of corticosteroids with or without an anti-proliferative agent for lymphocytes (mycophenolate mofetil or azathioprine). Less frequently, antibodies to T cells or to the interleukin-2 receptor are used initially as part of an induction protocol. Data supporting the superiority of any given baseline immunosuppressive agent are limited. Most studies have shown that the severity of recurrent HCV is similar whether cyclosporine- or tacrolimus-based immunosuppression is used[32,34–36]. Data on mycophenolate mofetil are conflicting: some reports show improved outcomes, whereas others show worse outcomes[37,38]. Most results indicate that it is the overall intensity of immunosuppression that affects outcomes: more intense immunosuppression leads to worse outcomes. Thus, HCV-induced graft failure, progression to cirrhosis and severe cholestatic hepatitis are more common in recipients who receive high-dose bolus steroids and anti-lymphocyte and anti-interleukin-2 receptor antibody preparations[32,39].

These agents, however, are usually used to treat organ rejection. Treatment for rejection has been associated with diminished survival in HCV-positive but not HCV-negative recipients[40]. Because almost all individuals have some degree of recurrent HCV with portal inflammation, differentiating between rejection in the setting of recurrent HCV and HCV recurrence alone can be difficult on biopsy and requires a skilled hepatopathologist. Certain features (such as lobular activity and interface hepatitis) are more compatible with hepatitis C, whereas others (such as bile duct damage and mixed cellular infil-

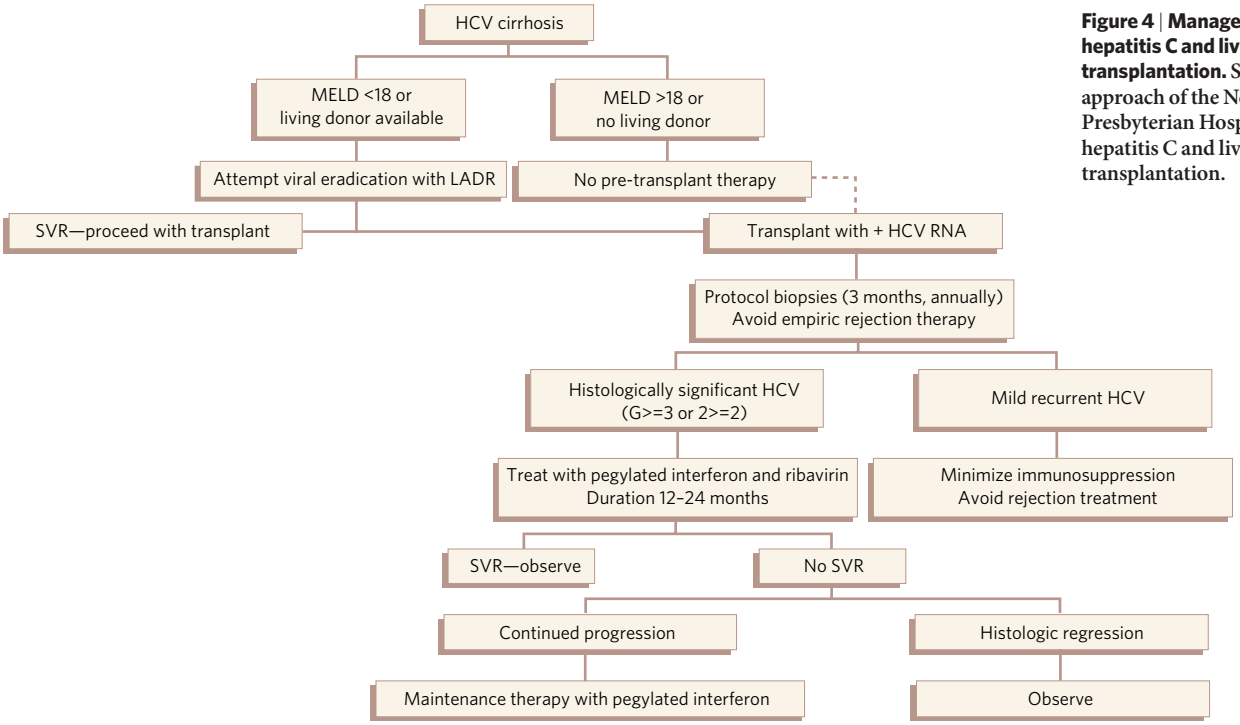

Figure 4 | Management of hepatitis C and liver transplantation. Shown is the approach of the New York Presbyterian Hospital to hepatitis C and liver transplantation.

trates) suggest rejection, but there is considerable overlap. Therefore, modulating immunosuppression in the setting of suspected mild rejection by either increasing the dose or substituting the calcineurin inhibitor and/or reintroducing mycophenolic acid may be preferable to using bolus glucocorticoids and/or antibodies to T cells.

Rapidly tapering doses of steroids and steroid-free immunosuppression with or without induction antibodies have been thought to reduce the likelihood of severe recurrent HCV. The latter may be preferable because high-dose steroids are avoided completely and preliminary data support its use[41]. The emerging consensus is that rapid changes in immunosuppressive level are most deleterious because they facilitate increased viral replication during intense immunosuppression, followed by immune recognition and clearance of virally infected allograft cells during rapid immunosuppressive withdrawal. Thus, our approach at New York Presbyterian Hospital has been to choose adequate immunosuppression to minimize the incidence of rejection, followed by a very gradual taper, and to avoid intense treatment for rejection with bolus steroids or antibodies. We use a calcineurin inhibitor (either cyclosporine or tacrolimus) and a slow taper of steroids over 6–12 months with mycophenolate mofetil for the first year, and take protocol biopsies at months 3, 12 and 24 to guide our decisions on immunosuppressive and antiviral treatment (Fig. 4).

Retransplantation for recurrent HCV

Because the recurrence of HCV is often accelerated after transplantation, the issue of whether to retransplant individuals with graft failure caused by recurrent HCV is highly controversial. The approach to retransplantation for recurrent HCV varies widely, and some centres no longer perform the procedure owing to poor recipient and graft survival. Individuals undergoing retransplantation for HCV have worse outcomes than do those undergoing primary transplantations; however, the outcomes are not clearly worse than those after retransplantation for other causes. Thus, it does not seem reasonable to exclude all individuals with recurrent HCV from retransplantation. Those with early, aggressive recurrence and graft failure within the first year, however, have very poor outcomes after retransplantation, as do those with very high MELD scores. These individuals should not undergo repeat transplantation except under highly selected conditions.

Treatment of hepatitis C in the peri-transplant period

Both the optimal timing and method of treating recurrent HCV after liver transplantation have been studied inadequately, but treating individuals when they are on the waiting list and pre-transplant viral eradication, respectively, represent the ideal. With pegylated interferon and ribavirin therapy, individuals with compensated cirrhosis were found to have an end-of-treatment viral response and a sustained viral response (SVR) of 23% and 11%, respectively, in the NIH-sponsored HALT-C trial[42].

By contrast, the treatment of individuals with decompensated liver disease, who comprise most potential transplant recipients, has been far less promising. This strategy has been associated with exacerbation of encephalopathy, infection and other serious, adverse events with up to 10% mortality, as well as a low SVR[43]. However, an initial therapy of low-dose interferon (including pegylated interferon preparations) and ribavirin, followed by a slow escalation in dose, may be associated with improved tolerability and efficacy in individuals with compensated cirrhosis[42]. This strategy has been associated with a lower incidence of adverse events, but with a discontinuation rate of 27% (ref. 44). The on-treatment viral response and SVR were reported to be 39% and 20%, respectively, in 91 subjects[44]. A preliminary study of ten individuals suggests that those who achieve an SVR, or who are transplanted while on therapy with an undetectable viral load, have a less than 10% likelihood of HCV recurrence[45]. This is particularly useful with LDLT because it allows timed transplantation during therapy in individuals with lower MELD scores after viral clearance in the serum without a risk of post-treatment relapse. This approach could potentially cure about 40% of individuals with HCV who undergo LDLT.

After liver transplantation, both pre-emptive therapy before the development of histological injury and directed therapy after injury occurs have been attempted with varying success. After transplantation, the tolerability of interferon preparations and ribavirin is suboptimal: significant leukopenia and anaemia are common and multifactorial, both arising from drug-induced bone marrow suppression and renal insufficiency, which potentiates ribavirin-induced haemolysis[46]. Pre-emptive strategies using standard interferon and ribavirin have been associated with an on-therapy viral clearance of 23–40%, a sustained viral clearance of about 20% and a discontinuation rate of 12–50% (refs 47–49). A recent randomized trial of

pegylated interferon and ribavirin showed an SVR of only 8% with an early discontinuation rate of 31% (ref. 50). Treatment of established recurrent HCV has yielded an on-therapy response of 15–48% and an SVR of 7–26%, and has a discontinuation rate of 30–50% (refs 50–55). Longer-term treatment may improve the SVR, and many groups including ours use 18–24 months of therapy in individuals who achieve initial viral clearance.

Because sustained viral clearance is achieved in less than 30% of individuals, modulating the severity of disease and preventing graft loss are the goal. This has led to the use of maintenance therapy in many individuals, although controlled data supporting histological benefit in the absence of viral clearance are lacking. In addition, emerging data indicate that rejection increases with interferon treatment, particularly treatment associated with viral clearance[53,55]. For example, two studies have shown acute cellular rejection in 8 out of 23 and 5 out of 44 individuals treated with interferon or pegylated interferon, coupled with a high proportion of graft cirrhosis or failure[51,53]. In one study[53], four out of five individuals with rejection had viral clearance, an observation that others have noted anecdotally. This has led most groups to abandon pre-emptive therapy in favour of treating histologically significant disease.

The International Liver Transplantation Society has recommended that therapy should be initiated for all individuals with stage II fibrosis[56]. Our group initiates therapy for those with grade III–IV (moderate to severe) inflammation or stage II hepatitis (Fig. 4). The use of histological triggers for initiating therapy requires careful surveillance and protocol biopsies. Research is currently focused on defining the appropriate timing, dosing and duration of treatment, and the outcomes.

Future directions

Transplantation for end-stage liver disease is a life-saving therapy to reverse the manifestations of liver failure, portal hypertension and hepatocellular carcinoma. Its application is limited primarily by the shortage of organs. Despite the successful use of grafts from older, HCV-positive and living donors, organ demand will continue to outstrip supply until adequate xenografts or hepatic stem cells can be used.

Recurrent HCV does not affect short-term survival, but the more rapid progression of disease can lead to graft loss and can lower recipient survival 3–5 years after transplantation. Increased understanding of the interaction between hepatitis C and rejection, coupled with improvements in immunosuppressive strategies, pre- and post-transplant antiviral treatments and anti-fibrotic therapy, is desperately needed to improve outcomes. Appropriate donor and graft selection, careful monitoring with protocol liver biopsies and avoidance of excess immunosuppression are crucial. Given the current suboptimal results with antiviral treatment, prevention of significant histological recurrent HCV is the preferred strategy. ■

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