Gut

Hepatitis C and liver transplantation

Introduction

Cirrhosis secondary to hepatitis C virus (HCV) infection, alone or in combination with alcohol, is the principal indication for liver transplantation among adults, and is responsible for about half the transplants performed in many centres.[1 2] This may mean that a subset of the approximately 300 million people worldwide infected with HCV will progress to cirrhosis, liver failure, and would need a transplant in the future.[3] As there is no universally effective antiviral treatment, it is expected that demand will soon outstrip the already limited donor organ supply.

Some facts about HCV infection and liver transplantation have been substantiated since the end of 1998. (*a*) HCV infection (as defined by detectable viraemia) will occur universally after liver transplantation among patients who are viraemic before transplantation[4]; (*b*) de novo HCV infection is rare but may still occur even though blood products are screened[5]; (*c*) HCV related graft disease develops in the majority of patients followed for at least five years after transplantation[6 7]; (*d*) the natural history of hepatitis C, measured histologically, is variable and ranges from minimal damage to fibrosing cholestatic hepatitis[6–8]; (*e*) there is a lack of effective prophylactic treatments aimed at the prevention of recurrent disease; (*f*) current antivirals in the treatment of post-transplant HCV disease are of limited efficacy.[9–14]

A number of important issues still need to be investigated, including: (*a*) study of the causes of the decreasing mortality rate seen in HCV infected patients awaiting liver transplantation, particularly with the use of HCV infected organ donors and/or antiviral drugs before transplantation; (*b*) better understanding of the long term outcome of transplant recipients with HCV, and the factors associated with disease progression; (*c*) improvement of the management of recurrent HCV disease, with emphasis on immunosuppression; (*d*) evaluation of new approaches in the prevention and/or treatment of recurrent HCV infection, and the effectiveness of combined interferon (IFN)/ribavirin treatment soon after liver transplantation; (*e*) retransplantation in patients with allograft failure resulting from recurrent HCV disease.

Natural history of hepatitis C virus infection after liver transplantation

There is no uniform definition of recurrent hepatitis C and this has impaired interpretation of results of different studies, despite an increasing interest in the evaluation of the natural history of HCV infection in liver transplant patients. Recurrent HCV is defined in four different ways but there is no distinct differentiation between the various types (serological, biochemical, virological, and histologi-cal). The universal definition of recurrent HCV infection is persistence of the virus as detected by molecular techniques,[4] whereas recurrent disease is defined by the evidence of histological hepatitis in 50–70% of recipients after a mean follow up of two years.[6–8 15 16] However, 30–50% of patients with short term follow up may be viraemic without disease.[8] Definitions based on biochemical or serological markers may be inaccurate as altered liver function tests in the transplant patients clearly lack specificity,[6 7] and serological assays[17 18] are relatively insensitive, both before and after transplantation. Transplantation impairs antibody production but serum HCV RNA is consistently detected and levels of viraemia after transplantation are higher compared with pretransplant values.[5 19 20] Short term follow up shows that post-transplantation HCV infection is a relatively benign condition,[6–8 15 16] but a longer follow up of five to seven years indicates that 8–30% of the patients develop cirrhosis.[6 7] Accelerated liver injury leading to rapid development of liver failure has been observed in a small proportion of patients (<5%).[21] Similar liver injury has been described previously in hepatitis B virus (HBV) infected patients with fibrosing cholestatic hepatitis.

Although the median term survival rate of HCV infected patients is similar to that of uninfected controls,[6 22] published series have yet to include enough patients to detect minor differences in outcome. Furthermore, factors which potentially affect the natural history of HCV, and are present both before and after liver transplantation, are often not identified or have not been included in most published series. Finally, the duration of follow up in previous studies may not be sufficient to detect differences in outcomes, as full manifestation of HCV related liver disease may not be apparent until after a prolonged period of infection. In a recent study, protocol biopsy samples were taken annually from all HCV infected patients. The percentage of patients reaching fibrosis scores of 3 or 4 increased significantly with time (there was an actuarial rate of HCV cirrhosis of 8.5%, 16%, and 28% at two, three, and five years, respectively).[7] The annual rate of fibrosis progression may be higher[23] than reported in the non-transplant population,[3] suggesting that the length of time needed to develop significant HCV related liver damage could be shorter in immunosuppressed patients than in immunocompetent ones.

Currently, good short and medium term survival rates warrant continued transplantation in this group of patients.

However, patients with an increased risk of severe disease after transplantation should be better defined in order to improve their management.

Retransplantation

Recently as a result of an increase in the number of HCV infected recipients in need of retransplantation, it has become vital to determine whether all patients with graft failure due to recurrent HCV disease are candidates for further transplantation. Early reports suggested poor outcome in this group of patients,[21] but more recent studies have reported improved outcome, particularly when retransplantation is performed before development of infectious and renal complications.[24 25] The severity of recurrent HCV disease in the second graft does not seem to be related to the severity of disease in the first.[24 25] The increasing shortage of organ donors and the growing numbers of patients in need of first transplantation will have severe consequences on the candidacy of patients being considered for retransplantation.

Factors influencing disease severity and disease progression

The factors influencing the rate of disease progression are largely unknown, but may relate to the characteristics of the infecting viral strains, the genetically determined characteristics of the infected individual, or environmental and/or iatrogenic influences on the infected individual—for example, immunosuppression or alcohol consumption.

HCV GENOTYPES

Conflicting studies have evaluated the relation between severity of liver disease after transplantation and HCV genotypes. Some,[6 26] but not all,[27–29] have implicated genotype 1 (and in particular subtype 1b) in more aggressive post-transplantation disease. This may be influenced by differences in genotype distribution in the study population, differences in genotyping methods, the presence of unmeasured confounding variables such as type and amount of administered immunosuppression, length of histological follow up, and differences in case definition (histological disease severity versus patient or graft survival).

HCV RNA LEVELS

Studies of the association between the level of viraemia and disease severity have produced contrasting findings.[5 19 20 30] Differences in methods of handling and storing serum samples, methods for quantitation, genotype distribution, definitions of disease severity, study design (cross sectional versus longitudinal), and time of HCV RNA measurement and histological assessment may all contribute to these discrepancies. Most cross sectional studies have documented a lack of correlation between HCV RNA levels and disease severity, suggesting an immune mediated mechanism in chronic liver injury.[5 19] However, high levels of viraemia have been detected in patients with fibrosing cholestatic hepatitis and during the acute phase of recurrent hepatitis C.[5 30 31] Thus, liver damage may be due to the direct cytopathic effect of HCV during the early phase of recurrent hepatitis C.[30 31] Furthermore, in an attempt to define the early parameters which may be predictive of histological progression, some studies have suggested that the estimation of levels of viraemia before and soon after transplantation may predict the occurrence and/or severity of hepatitis C in the graft.[20 23 29 30]

HCV DIVERSITY

Studies of both immunocompetent and immunocompromised patients suggest that HCV heterogeneity plays a role in the pathogenesis of progressive HCV disease.[32 33] However, the results from these studies are inconclusive and somewhat discrepant, and may be related to the small number of patients included, the different methodologies applied to assess HCV heterogeneity (single strand conformation polymorphism, heteroduplex mobility assay, sequencing), the type of end point chosen (viral complexity, viral diversity, or viral divergence), the region of the genome evaluated, and the definition of disease severity.

IMMUNOSUPPRESSION

There are conflicting results on the association between administered immunosuppression and disease severity[6 23 34]; this warrants prospective studies comparing different types of immunosuppression based regimens in HCV infected recipients.

In contrast, both a higher incidence of recurrent hepatitis C and more aggressive disease have been linked with rejection and the treatment of rejection with more potent immunosuppression.[35–37]

OTHER FACTORS

In some studies, necroinflammatory activity and fibrosis grading as seen on the initial liver biopsy sample, have been used as variable predictors of subsequent development of severe chronic hepatitis C.[7 30 38] Some,[39] but not all studies,[6] have suggested that although HLA-B sharing between the donor and the recipient reduces the incidence of acute cellular rejection, it also promotes the recurrence of viral hepatitis in liver transplant recipients. Thus, patients who develop cytomegalovirus viraemia could be at increased risk of severe HCV recurrence.[40] In contrast, coinfection with other viruses, such as HBV[41] or hepatitis G virus (HGV),[42] does not seem to influence the post-transplantation course of HCV disease. Race also influences outcome in patients with recurrent HCV infection—non-whites have more aggressive disease than whites.[23 29] This association deserves further analysis both in immunosuppressed and immunocompetent patients.

Recognition of patients at high risk of severe outcome after transplant is desirable as these patients can be targeted for intervention. However, it is not possible to predict accurately which patient will develop serious disease after transplantation and which will not. Currently, HCV RNA levels before and early after transplantation, severe and early acute hepatitis, and strong immunosuppression seem to be the variables most consistently associated with poor outcome; further analysis is needed to verify these findings.

Patient management

Prevention of HCV recurrence is the principal aim in the treatment of these patients but current treatments are ineffective. Kasahara *et al* showed that polyclonal immunoglobulins containing anti-HCV, analogous to the use of hepatitis immune globulin in preventing HBV recurrence, decreased the incidence of recurrent HCV viraemia one year after transplant.[43] However, different approaches to treatment may be necessary as the humoral immune system fails to provide adequate and long lasting neutralising immunity against HCV. There are four potential alternative and/or complementary approaches: (*a*) preemptive antiviral therapy with the aim of suppressing viral replication so that the risk of aggressive recurrent HCV disease is reduced while the patient awaits a donor organ; (*b*) antiviral therapy soon after transplant in an attempt to prevent progression of HCV related graft disease before histological damage has occurred; (*c*) treatment of disease when and if it does occur; and (*d*) changes in patient management as some factors—for example, immunosuppression, have been associated with more severe disease.

PREEMPTIVE THERAPY

Pretransplantation antiviral therapy may be attempted to improve hepatic function, and thus eliminate or delay the need for transplantation. However, there are no convincing data suggesting that IFN alone or in combination with ribavirin, is capable of improving hepatic function in decompensated cirrhotic patients. Some studies have suggested that the incidence of both hepatocellular carcinoma and hepatic decompensation are reduced among compensated cirrhotic patients treated with IFN, which supports the need for further clinical trials of this treatment.[44–46] Trials are currently underway to assess the use of combination therapy in decompensated patients and are based on the improved efficacy of combination therapy compared with monotherapy in chronic HCV infected patients.[47] Alternatively, pretransplant antiviral therapy may be used preemptively in order to alter the post-transplantation course as both HCV RNA levels before and soon after transplantation have been shown to influence disease progression and post-transplantation outcome.[6 23 29 30] Interferon alone, or in combination with ribavirin, has been shown to decrease viral load in cirrhotic and transplant patients. Thus, combination therapy may represent a reasonable approach towards minimising the severity of post-transplant disease. The role of combination therapy in patients with hepatic decompensation should be studied prospectively and this approach should be used clinically with extreme caution.

Preemptive therapy soon after transplantation with IFN alone,[48 49] or combined with ribavirin,[50] has also been attempted to reduce the incidence and/or severity of recurrent hepatitis C. In one study,[48] 86 recipients were allocated randomly, within two weeks of transplantation, to receive either IFN alone (n=38) or placebo (n=48) for one year. Although patient and graft survival two years after transplantation did not differ between groups and the rate of viral persistence was not affected by treatment, histological disease recurrence was observed less frequently in those patients who had received IFN (eight of 30 who could be evaluated at one year) than in those who were not treated (22 of 41; p=0.01). In a second controlled trial,[49] 24 recipients were allocated randomly, two weeks after transplantation, to receive IFN or placebo for six months. No difference in graft or patient survival was observed. Although both the incidence of histological recurrence and its severity did not differ between groups, a delay in the development of HCV hepatitis was observed among treated patients (408 versus 193 days, p=0.05).

In a case series,[50] 21 recipients were treated with IFN-α2b and ribavirin starting three weeks after transplantation. After a median follow up of 12 months, four (19%) patients had developed acute recurrent hepatitis C, but only one (5%) had progressed to chronic active hepatitis, despite the presence of viraemia in 59% of patients.

These results are promising and warrant multicentre trials to evaluate this treatment. Whether early preemptive treatment reduces the likelihood of post-transplant disease or simply delays development is still under evaluation.

TREATMENT OF HCV RELATED GRAFT DISEASE

Treatment of recurrent HCV disease with IFN or ribavirin as single agents has thus far been disappointing, but initial results from combination therapy are encouraging.

A regimen of 3 MU IFN alone three times a week for six months failed to clear serum HCV RNA, despite transiently normal alanine aminotransferase (ALT) values in a subset of patients treated (0–28%), with minor or no histological improvement.[9 10] Moreover, as IFN can upregulate the expression of HLA class I and II, which may, in turn, increase the risk of allograft rejection, there is concern about using IFN in solid organ transplant recipients. However, in contrast to the renal transplantation, IFN induced rejection seems to be rare in liver transplantation.

In order to improve the sustained virological, biochemical, and histological response rate, several approaches have been tried. Prolonged IFN therapy was described in one small uncontrolled study,[51] in which patients were treated for a mean of 21 months with apparent good biochemical, but not virological, response rates. Ribavirin monotherapy has been also evaluated in liver transplant recipients, with biochemical improvement observed in many, but virological clearance seen in none.[11 12] There was universal relapse after withdrawal and no histological improvement was seen. The main side effect was haemolysis which resolved after treatment ended. One randomised trial compared 12 months of ribavirin versus IFN monotherapy in 30 liver transplant recipients.[13] Although ribavirin was superior in achieving biochemical response (93 versus 43%, p<0.01), only patients treated with IFN had reduced HCV RNA levels. No histological improvement was observed in either group.

Recently, research has concentrated on combination therapy and initial results have been promising.[14] In a non-randomised pilot study, 21 patients with early documented recurrent HCV disease were treated with IFN-α2b (3 MU three times a week) and ribavirin (1000 mg/day) for six months, and then maintained on ribavirin monotherapy until the end of the study. ALT values returned to normal in all patients and 50% cleared HCV RNA from serum at the end of the combination treatment period. The remaining patients, although viraemic, experienced a 50% reduction in viral load. Only one patient had a biochemical relapse during the six month period on ribavirin alone, despite reappearance of serum HCV RNA in 50% who had initially cleared HCV RNA. Most importantly, all patients but one, who tolerated the drug showed an improvement in liver histology. Safety and tolerance were satisfactory, and the most common side effect was reversible haemolytic anaemia; no patient experienced graft rejection. This favourable outcome is noteworthy because all patients had high HCV RNA levels before treatment (mean value of 125 Meq/ml) and 92% were infected with HCV genotype 1, which is classically associated with lack of response to treatment. Off treatment response rates were not provided in this initial report, but maintenance with ribavirin is potentially important to avoid relapse. Whether maintenance treatment could be discontinued in patients who have responded virologically still needs to be determined. The encouraging results from the pilot study of combination treatment indicate a need for randomised controlled trials, several of which are currently underway.

MANAGEMENT OF IMMUNOSUPPRESSION

When managing this patient population, hepatologists and surgeons have great difficulty in deciding the best induction and maintenance immunosuppression regimen. Treatment of rejection is difficult as the symptoms may be similar for both rejection and recurrent disease. Most studies have found no differences in patient and/or graft survival in those treated with cyclosporin based compared with those treated with tacrolimus based induction regimens.[6 29 34] Prospective trials are underway to assess this. The more severe liver disease described in patients treated with a high number of methylprednisolone boluses and/or OKT3 suggests that rejection treatment should be less aggressive in these patients, a trend already followed in many transplant centres.[35–37] Additionally, serial biopsy samples should be taken when there is doubt between

rejection and recurrence as a result of atypical histological findings (notable ductal injury and venulitis). Lymphoid aggregates, fatty changes, and sinusoidal dilatation are more suggestive of HCV infection whereas rejection is indicated by endothelitis, bile duct necrosis, and a mixed portal inflammatory infiltrate (eosinophils and neutrophils as well as mononuclear cells).[8] The date of transplantation may be relevant in interpreting test results as non-hepatitis biopsy findings are usually seen earlier than acute and chronic hepatitis findings, which are rarely seen within the first month after transplantation.[52] A therapeutic trial with a short course of steroids has been proposed as a way to differentiate between rejection and recurrent hepatitis C but this treatment may be detrimental in the long term, and is thus not recommended at the present time. If test results indicate the presence of both rejection and recurrent hepatitis C, treatment with corticosteroids may be appropriate.

Conclusion

In spite of universal viral recurrence, early post-transplantation infection usually results in indolent disease with good graft and patient survival, compared with the prognosis for other patients undergoing transplantation for non-viral end stage liver disease. However, the full consequences of HCV recurrence are becoming apparent with the observation that liver failure occurs with longer follow up in a proportion of patients.

The evidence that recurrent HCV disease is an important cause of morbidity and even mortality in liver transplant recipients has led to an evaluation of treatment for this disease. Unfortunately, neither IFN nor ribavirin, when given as single agents, have been significantly successful. Recently, encouraging results have been described with combination treatment when used both preemptively and therapeutically. Multicentre trials are ongoing to evaluate further these approaches to treatment. Additionally, the end points used to define how successful treatment has been should reevaluated for liver transplant patients; this process has recently been undertaken in immunocompetent patients. The inability of current antiviral treatment to eliminate HCV in liver transplant patients may not necessarily imply a failure of treatment. Indefinite treatment designed to suppress the effects of the virus may be needed if a reduction in histological disease progression, or improved graft and patient survival, is to be seen. New long lasting formulations of IFN, which need only one dose weekly, may improve patient compliance. Toxicity, cost, and resistance issues should be tackled before this approach is considered. Ultimately, development of potent antivirals to be given either before or after liver transplantation will change the course of post-transplant disease and hopefully obviate the need for liver transplantation in patients with advanced HCV disease.

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