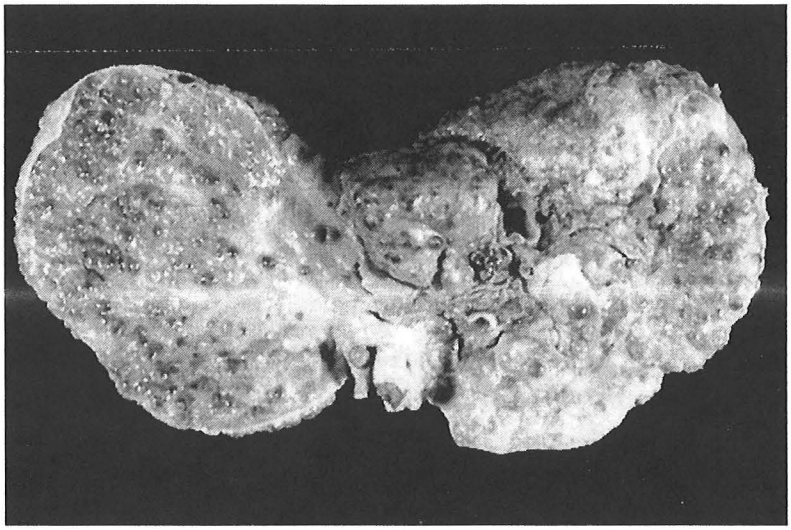
Hepatitis C:
Transplantation Dilemmas



(Inpharm.com)

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Mr. H is a 55 yo white male with past history of intravenous drug abuse, alcohol abuse and hepatitis C with cirrhosis complicated by variceal bleeds and hepatic encephalopathy who underwent an orthotopic liver transplant (OLTx) on 7/11/98. His course has been complicated by a history of CMV infection two months after his transplant. In 10/00, he was noted to have recurrent hepatitis C with an HCV RNA level of 800,000 and an HCV genotype of 1B. The liver biopsy demonstrated stage 2 fibrosis and grade 3 activity. Ultrasound was notable for an atrophic pancreas, normal kidneys and s/p cholecystectomy. Creatinine clearance was 50cc/min. Medications included cyclosporine, furosemide and terazosin. In August 2001, his laboratory values were notable for WBC 3.8 K/cu mm; Hgb 12.8 g/dl; Platelets 128K /cu mm; Cyclosporine levels 186 ng/ml; Creatinine 1.9 g/dl; AST 107 IU/ml and ALT 155 IU/ml.

Dilemma: S/P OLTx with recurrent hepatitis C and renal insufficiency

Mr. C is a 61 yo AAM with history of DM X 20 years, HTN X 20 years, CAD, S/P MI, 2 vessel CABG 1993, 4 vessel CABG 1999, PTCA with stent 2000. In 1974, he had severe burns requiring multiple skin grafts and blood transfusions and was noted in 1993 to have hepatitis C. He was tried on interferon alone for six months and combination interferon/ribavirin for seven months in 1998. He underwent a cadaveric renal transplant (CRT) 5/7/99 and now presents with rising LFT's. His HCV RNA is positive. Medication: Neoral 225/200 mg PE: Large areas of scarring over entire body from burns and skin grafts. Abdomen: S/NT/ND; no HSM, well-healed oblique scar RLQ. His laboratory values are notable for Creatinine 2.0 g/dl TP 7.9 g/dl, Alb 3.9 g/dl, INR 1.0 Alkaline phosphatase 175 IU/ml, AST 60 IU/ml rising to 100 IU/ml, ALT 64 IU/ml rising to120 IU/ml.

Dilemma: S/P CRT, Hepatitis C with rising transaminases.

These cases represent dilemmas that are facing physicians involved with transplantation and hepatitis C. The purpose of this protocol is to examine the diagnosis, the natural history of hepatitis C after transplantation, examine the factors that affect the natural history and finally, to examine the current treatment options for recurrent hepatitis C in liver and kidney transplant recipients.

LIVER TRANSPLANTATION

Recently, end-stage liver disease resulting from hepatitis C infection became one of the most common indications for orthotopic liver transplantation in the United States. According to the UNOS Liver Transplantation Registry, HCV, as an indication for liver transplantation, surpassed alcoholic liver disease as the single most common diagnosis in 1993 (1). One fourth of those patients undergoing liver transplantation had HCV infection. Furthermore, in the year 2000, HCV related liver disease accounted for approximately half of the transplantations in many centers (~4,500 transplants in 2000) (figure 1)(2). The prevalence of HCV in the U.S. according to the NHANES III survey was 1.8% and 20% of these patients may progress to cirrhosis Thus, 0.36% of 280 million people or approximately 1 million people may progress to HCV cirrhosis (3). Orthotopic liver transplantation may be required by all of these patients.

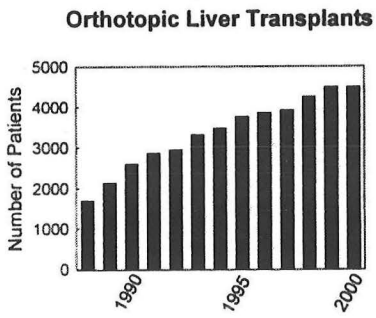


Figure 1

Investigators have examined the rate of survival after orthotopic liver transplantation for patients with hepatitis C and compared them to the survival rates after liver transplantation for other liver diseases. The five year survival rates were 77.2%, 65.3%, 34.5% and 79.4 % for autoimmune hepatitis, chronic viral hepatitis, hepatoma, and primary biliary cirrhosis (figure 2) (2). In a data base involving the transplant centers in Omaha, San Francisco and Mayo, patient survival for HCV infected patients was 70% 6 years post-OLTx, significantly worse than cholestatic diseases and significantly better than HBV or malignancies (4). Though the transplantation survival of patients who have hepatitis C was relatively high, these data suggest that the survival s/p liver transplant for hepatitis C can be improved. Recurrent hepatitis C status post liver transplantation accounted for the decrease in survival.

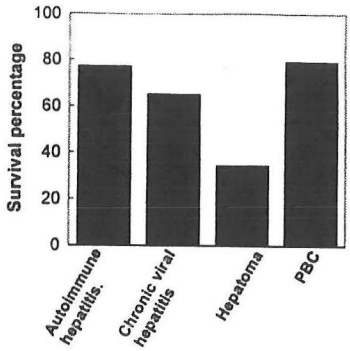


Figure 2

DIAGNOSIS OF RECURRENT HEPATITIS C

Recurrent HCV infection after orthotopic liver transplantation was initially demonstrated in 1991, when Martin et al reported anti-HCV positivity (EIA1) at 1-year follow-up in 5/6 patients who were anti-HCV positive pre transplantation, with histologic evidence of chronic hepatitis in three of them and graft loss in one (5). It is now recognized that recurrent infection is almost universal in patients who are viremic pretransplantation (6,7). Conclusive evidence of recurrence of HCV infection after liver transplantation came from detailed virologic work by Feray et al (8). In this study, pre and post-transplantation serum samples had a high degree of nucleotide sequence homology (95%) of the hypervariable region (E2/NS1) of the HCV virus.(8).

Following liver transplantation, HCV RNA levels begin to rise on day 2 reaching pre transplant levels on day 9 and become three times pretransplant levels by day 28. HCV RNA levels may ultimately reach 14 times pretransplant levels (9).

Viral levels tend to runs 10-20 folds higher posttransplant compared to pretransplant when quantitative studies such as the Chiron branched chain DNA assays are utilized (10). Furthermore, viral RNA can be detected in the liver during the first posttransplant month (11). More recently it has been suggested that the detection of IgM anti-HCV core may be a sensitive marker of viral recurrence, independent of the level of immunosuppression. Its measurement might provide early evidence of graft hepatitis (12).

Reliable quantitation of viral RNA using techniques such as the branched chain DNA assay may also prove to be useful for the investigation of recurrent infection after transplantation. For instance, the lobular hepatitis observed after recurrent infection may be associated with an extremely high serum viral titre (13). Therefore, measurement of viral titers may permit the early diagnosis of recurrent hepatitis, and may influence subsequent patient management (including the early administration and subsequent adjustment of antiviral treatment).

NATURAL HISTORY OF HCV INFECTION POST TRANSPLANTATION

Recurrent infection after liver transplantation defined as the presence of virus in the serum is universal (14). Although histologic evidence of liver injury will develop in the majority within the first year post transplantation, severe graft dysfunction is rare in the short-term (15). With longer

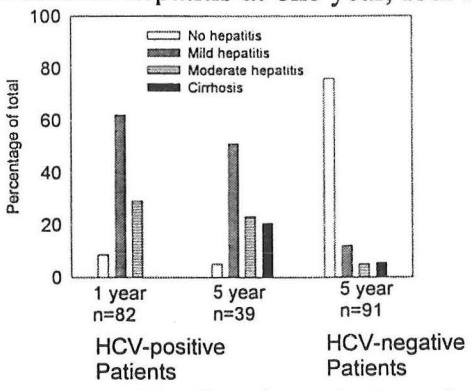
periods of follow up, a significant proportion of patients progress to cirrhosis (**5-30%**) after a median of **5 years** (16,17). The natural history of HCV infection appears to be shortened in liver transplant recipients compared with immunocompetent patients. There is some controversy on the effect of HCV on long term patient or graft survival when compared to that observed in patients undergoing transplantation for other nonmalignant indications (13, 16-21).

Importantly, information on the full effect of post transplantation HCV infection and factors that influence this natural history is incomplete. The observation that HCV reinfection occasionally leads to early graft loss, (5) whereas such rapidly progressive liver injury is rare in immunocompetent patients, suggests that an accelerated course may occur in some recipients. This type of injury (fibrosing cholestatic hepatitis) in which cirrhosis develops within a short time after OLTx occurs in 7.4% of patients (22).

The effect of HCV infection on graft and patient survival, independent of other factors that may influence outcome (such as the age of the patient and the UNOS status at the time of transplantation) has not been determined. Furthermore, most studies of outcome of HCV infection have included relatively small numbers of patients (up to 100) with relatively short durations of follow-up (3 to 10 years) (13, 16, 20, 23,24). The following studies examine the natural history of both end stage liver disease from cirrhosis and the rapid induction of fibrosing cholestatic hepatitis.

Compilation of Natural History Studies

In one study, liver-biopsy specimens were obtained as scheduled from 82 HCV-infected patients one year after transplantation and from 39 patients 5 years after transplantation. When the biopsy specimens obtained at 1 year were compared with those obtained at 5 years, there were no significant differences in the numbers of grafts without hepatitis (seven of 82 vs. 2 of 39), grafts with mild chronic hepatitis (51 of 82 vs. 20 of 39), and grafts with moderate chronic hepatitis (24 of 82 vs. 9 of 39). Eight patients had cirrhosis at 5 years. For 30 patients, biopsy specimens obtained at both 1 and 5 years were available. Of the 21 patients with mild chronic hepatitis at one year, four had moderate chronic hepatitis at 5 years and one had cirrhosis. In comparison, 6/9 patients with moderate chronic hepatitis at 1 year had cirrhosis at 5 years (16). These data suggest that patients with moderate chronic hepatitis at 1 year have a 67% chance of developing cirrhosis by 5 years. In the 130 patients with hepatitis C infection who survived more than six months after transplantation, 10 of 130 (5.4%) patients developed cirrhosis at a median of 51 months post transplant (16).



As a control, the investigator analyzed 91 HCV(-) liver-transplant recipients. Eleven patients had mild chronic hepatitis, 5 patients had moderate chronic hepatitis and 5 patients had cirrhosis (in the latter two groups, 7/10 were caused by recurrent hepatitis B). Thus, there was a significant difference at 5 years between the HCV-infected transplant recipients and the control group with respect to the incidence of cirrhosis and of mild and moderate chronic hepatitis (16).

A second investigator examined 81 liver biopsies from 19 patients, 14 of whom developed hepatitis and then separated the biopsies into three groups - no hepatitis, acute lobular hepatitis and

chronic hepatitis. The severity of the liver biopsy findings directly correlated with the time interval since transplant. Biopsies without hepatitis were seen early post transplant (usually in the first 30 days) whereas biopsies showing acute lobular hepatitis and chronic hepatitis were noted at averages of 135 days and 356 days (25). In another study, 67 patients had undergone transplant for hepatitis C. In this group of patients with a mean follow up of 22 months, 56% of the transplant recipients had developed clinical hepatitis, 29% had developed fibrosis or cirrhosis and four had required re transplantation for hepatitis C (26). In summary, 5.4-29% transplant recipients for HCV may develop cirrhosis anywhere between 22-51 months after orthotopic liver transplantation. Of interest, the highest rate of cirrhosis was noted in the study with the shortest follow up period.

In two more recent studies from Europe, one from Spain and one from Germany, suggest that different transplant centers may have different experiences in the natural history of hepatitis C. In a recent study from Spain, investigators examined 81 patients were followed after liver transplantation for hepatitis C. The genotype distribution after transplantation was 1b (n=73), 1a-1b(n=2), 1a -2(n=1) and 4 (n=2). The rate of HCV-related graft cirrhosis was 3.7% at 1 year, 8.5% at 2 years, 16% at 3 years and 28% at 4 and 5 years following OLTx(figure 4). Overall, patient survival was 95%, 91% and 84% at 2, 3 and 5 years, similar to the HCV noncirrhotic pts (97%, 94%, and 86%), but differing from those with graft cirrhosis (82%, 72% and 54%) (17).

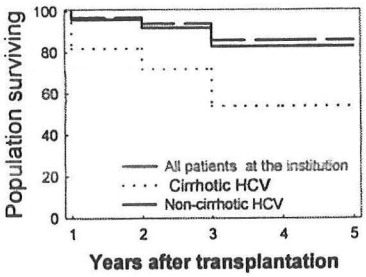


Figure 4

In contrast, one investigator followed 61 patients reinfected with HCV in comparison with all other patients transplanted for nonmalignant, non HCV related indication from November 1979 until March1, 1993 for as long as 12 years. The 2, 5 and 10 year survival rates were 67%, 62% and 62% for the hepatitis C reinfected patients and 62%, 57% and 52% for non-HCV patients, respectively (20). Therefore, the data from two European centers suggest that there are different rates of progression to cirrhosis and graft and patient survival.

Fibrosing Cholestatic Hepatitis C

A rare and severe form of cholestatic hepatitis C has been reported after orthotopic liver transplantation in patient with hepatitis C. It rapidly progresses to liver failure and requires re transplantation within 2 years in most cases. As early as 44 days after transplantation, one patient had evidence of cholestatic hepatitis C. By day 101, the cholestatic hepatitis C was severe with evidence of fibrous septa. The liver biopsy from this patient had evidence of thin perisinusoidal bands of fibrosis extending from portal tracts. This severe form of fibrosing cholestatic hepatitis C (FCHC) has been associated with geneotype 1 (27).

In another series, 10/135 (7.4%) developed FCHC. Ten patients with severe recurrent hepatitis C were identified; 1 died, 1 awaits retransplantation, and eight underwent retransplantation. All 10 developed severe progressive cholestatic hepatitis, with a mean rise in bilirubin to 24.7 mg/dl at the time of retransplantation. Histology at initial recurrence was of mild hepatitis without evidence of rejection. The failed grafts showed either cirrhosis or confluent hepatic necrosis. The onset of cholestasis preceded retransplantation by less than 5 months. In all cases, FCHC led to retransplant or death (22).

OUTCOME OF LIVER TRANSPLANT RECIPIENTS WITH SEVERE DISEASE

For patients that have developed graft cirrhosis, other investigators examined the cumulative probability of decompensation over time: 8% at 1 month, 17% at 6 months and 42% at 1 year (n=39). The median interval between stage 4 and decompensation was 7.8 mos, (4 days to 2.6 yrs). Most frequent event that signalled decompensation was ascites. Patient survival dropped significantly once decompensation developed 93, 61and 41% at 1,6 and 12 mos (figure 5).The mortality rate was low in compensated cirrhotic patients followed up for a short-medium term of approximately 1 year Variables associated with mortality include a short interval from transplantation to development of post transplantation cirrhosis, a high Child Pugh score and a low albumin at diagnosis of compensated cirrhosis (21).

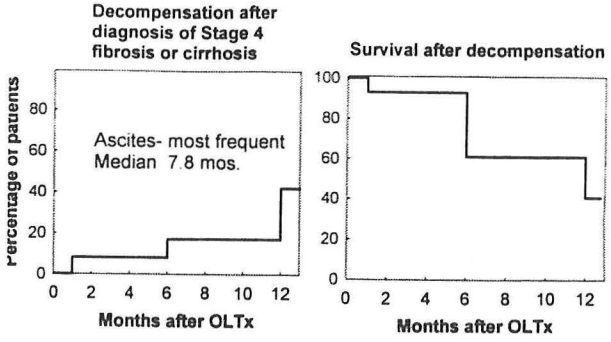


Figure 5

In summary, these studies suggest that the natural history of hepatitis C is variable. For patient who develop FCHC, rapid retransplantation within 24 months is necessary. For patients that have recurrent HCV, the percentage of patients that develop cirrhosis appears to increase with the time from transplant, approaching 30% at 5 years but may be as high as 50% in specific settings, depending upon various environmental and immunological factors. Once cirrhosis is noted, 50% of the patients will decompensate within a year. Finally, 50% of the patients with decompensation will die within the next year. Though graft and patient survival may not differ in the first 5-10 years, in the next 10 years, the loss of graft will likely be due to recurrent hepatitis C.

FACTORS THAT INFLUENCE SEVERITY OF RECURRENT HEPATITIS C

Factors that determine why some patients are more susceptible than others to recurrent infection and further liver damage are currently under investigation, and include type and amount of post transplant immunosuppression, episodes of rejection, size of viral inoculum, viral genotype, degree of HLA mismatch donor-recipient and episodes of rejection.

Steroids

In a controlled trial in patients with non-A, non-B hepatitis who had not undergone transplant, progression of liver disease was significantly greater in patients treated with steroids compared with untreated patients (28). The authors examined 52 patients for a median of 28 months to assess the natural history. Among eight patients treated with steroids, 6 patients underwent follow up liver biopsies. Quantitative analysis of inflammatory and fibrotic changes indicated significant progression of histological severity during a median of 33 months(7-98 months) between biopsies with cirrhosis developing in 4 of the patients. In contrast among seven untreated patients rebiopsied after a median of 16 months (11-37), there was no overall change in histological severity and 1 patient developed cirrhosis. This paper suggests that steroids may cause heightened progression of hepatitis C. In the transplant settings, augmented immunosuppression for treatment of rejection has been shown to be a particular risk factor for recurrence of hepatitis C.

Of interest, Charlton in the multicenter study reported that HCV transplant recipients with a mean daily steroid dose >100 mg in the first 42 days carried a significantly increased risk of death when compared to recipients with an average daily dose of 50 mg or less (19). However, the study

did not address whether the death was associated with recurrent hepatitis C or rejection.

Other immunosuppressive agents.

When cyclosporine was used to treat chronic hepatitis C in nontransplanted patients, there was a decrease in the alanine transferase (ALT), however, viral levels did not change during treatment, which suggests that the role of cyclosporine in recurrence was not as important as that of steroids. Early studies initially suggested that tacrolimus caused the progression of hepatitis C to be more rapid. For example, recurrence appeared to be more rapid in a small group of 9/96 patients who received tacrolimus for primary immunosuppression (29).

However, in one of the few randomized trials to compare tacrolimus with neoral for primary immunosuppression after transplantation for hepatitis C. Zervos et al (30) found more rejection episodes in the neoral group but no difference in the recurrence rate between the groups. Fifty consecutive HCV+ liver transplant recipients were randomly assigned to either tacrolimus or neoral based immunosuppression. Patient and graft survival rates in the two groups were 72% and 68% for the tacrolimus group and 67 and 64% for the cyclosporine at 417 days (figure 6). 4 patients in the tacrolimus group developed severe recurrent FCHC within 104 days (median) (range 50-137 days) after OLTx. 5 patients in the neoral group developed FCHC 10-220 days after transplantation (30). Furthermore, early results of the U.S. multicenter study involving 113 patients with HCV who were randomized to tacrolimus or neoral revealed no significant difference in 3 year patient survival rate.

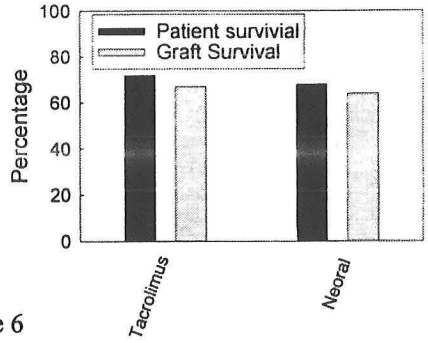


Figure 6

Johnson evaluated 67 patients after OLTX for evidence of recurrent HCV (4). Recurrent HCV infection, which developed in 38 patients (57%) was documented by using ELISA assay, PCR or b-DNA assay. Of these 38 patients, 31 (82%) had evidence of hepatitis on biopsy specimens. There was no significant difference in number of patients who received tacrolimus. However, the recurrent HCV disease seems more severe in patients receiving tacrolimus than in patients receiving cyclosporine or OKT3 (26).

Increased allograft rejection in patients infected with HCV has been alternately associated with the use of tacrolimus and cyclosporine. In other studies, the cumulative 1-year incidence of ACR was similar in patients receiving tacrolimus (+ steroids) and cyclosporine (+ steroids +/- azathiorpine) (75 vs 68% respectively (P=.94). However the cumulative 1 year incidence of steroid resistance rejection was 0 % for recipients receiving tacrolimus versus 22% for recipients receiving cyclosporine (p=.04 by exact log rank test). The increased incidence of SRR among recipients receiving cyclosporine based induction immunosuppression did not translate into increased graft loss or mortality (19).

Recurrence and number of rejection episodes (Steriod resistance)

Patients with steroid-resistant rejection appear to have a more aggressive course of HCV infection following liver transplantation than do others. Most studies have found a strong correlation between number of rejection episodes and the incidence of recurrent disease. In the first study, recurrence directly correlated with the number of rejection episodes. 6/33 patients (18.2%) with no rejection had HCV recurrence vs. 11/ 26 (43% with one rejection episode) and 26/37 (70% with more than one episode). 15/21 (71%) who required OKT3 for steroid resistant rejection(SRR) had recurrence versus 28/75 (37.3%) who either had no SRR or developed it after recurrence was

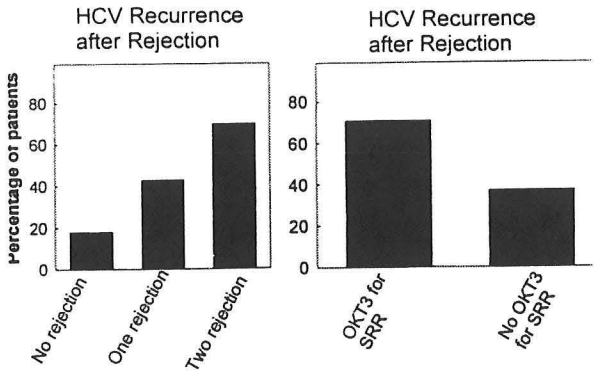


Figure 7

diagnosed (figure 7). Furthermore, patients who had SRR recurred earlier (127 days) than those who recurred but did not have SRR (246 days) (29).

Other investigators reported a higher recurrence rate in patient that received OKT3 for SRR Rosen et al compared 19 patients who received OKT3 for SRR to 33 matched controls who received steroids alone for rejection. 26.3 % who received OKT3 developed cirrhosis vs 6 % of 33 patients treated for SRR (31). A third study, however, could not demonstrate an association between use of either OKT3 or corticosteroid boluses with recurrent HCV disease. In this study, rejection episodes occurring within 6 months of transplantation were more common in patients with recurrent HCV than in those without recurrence (P = 0.011) (32).

In another study, 81 HCV + liver recipients were followed for an average of 32 months (17). The actuarial rate of cirrhosis in this study was 28% at 4 years. Rejection occurred more frequently in patients who developed cirrhosis (83%) than in those patients who did not develop cirrhosis (48%).

The relationship between rejection treatment and patient survival was investigated among the 166 HCV infected recipients in a multicenter study. Compared with patients not treated for rejection, being treated for acute cellular rejection (ACR) (RR = 2.9 and p=.03) and steroid resistant rejection (SRR) RR = 5.4 P=.0033) were independently associated with increased mortality. Acute rejection and SRR each increased the risk for mortality after transplantation for hepatitis C.(18). In combination, these studies demonstrate that recurrent rejection and the use of OKT3 cause an increase in recurrent HCV in post transplant recipients.

Controversial : Pretransplant Viral Load and Viral Genotype

There is controversy as to whether the pretransplantation level of viremia is predictive of reinfection (8,19,33, 24). Patients with high pretransplantation HCV-RNA titers tended to have higher levels posttransplantation as well. The level of HCV RNA does not correlate with the histologic severity of the liver injury. Interestingly, some patients with very high levels of virus have no histologic evidence of hepatitis, arguing against a direct cytopathic effect of HCV or that there is a substantial variation in host immune response to this virus (34).

Other investigators have argued that pre transplantation viral load has prognostic values for patients with hepatitis C. Investigators compared the pretransplantation HCV RNA titer of >1.0 $X10^6$ vEq/ml to an HCV RNA titer of <1.0 $X10^6$ vEq/ml. The percentage of patients who either died or required retransplantation because of recurrent HCV was 32% among those recipients with an HCV RNA titer of >1.0 x 10^6Veq/ml vs 10 % among HCV infected recipients of HCV RNA titer of <1.0 x 10^6 Veq /ml (19).

Two other studies failed to demonstrate an association between the level of viremia and disease severity (24, 33). However, in prospective longitudinal studies, high levels of HCV RNA were associated with acute (13) or chronic recurrent hepatitis(35).

The influence of viral genotype on disease severity also remains controversial. Infection with genotype 1b has been associated with more severe recurrent disease than infection with non-1b genotypes in two studies (16, 23). However, in two other studies, genotype did not correlated with

severe recurrent disease (20, 24). Ferry et al observed that patients infected with genotype 1b had severe hepatitis, but survival was unchanged (19). Similarly, Zhou et al found no effect of genotype on survival (24).

Controversial factors: HLA matching

Matching of the specific loci of the HLA appears to be important in some studies but not in others. One study examined18 HCV infected OLTx recipients with chronic active hepatitis(CAH) at 1 year post transplantation. A significant association between donor recipient matches at 1 or 2 HLA DQβ locus was strongly associated with the recurrence of CAH following liver transplantation for end stage HCV infection (36).

HISTOLOGY

As indicated earlier, the progression to cirrhosis appears to progress through a number of histological stages of hepatitis, bridging fibrosis and finally cirrhosis. Alternatively, in a small group of patients, the progression is rapid, a fibrosing cholestatic hepatitis. For example, in one series of 135 patients with HCV-related cirrhosis who underwent transplantation, 10 (9%) patients developed cholestatic hepatitis and severe liver dysfunction, with a mean time of 4 months from onset of cholestasis to retransplantation (22).

In general, in patients who are HCV-RNA positive after transplantation, 43% to 67% have histologic evidence of hepatitis within 1 year (14, 15, 37, 38). Among viremic patients with histologic evidence of hepatitis, 70-80% have relatively mild disease and only 20-30% have significant fibrosis or cirrhosis at 5 years. Serum ALT levels are normal in 50% of those with evidence of hepatitis on biopsy, indicating that liver enzymes are not a reliable marker of liver injury.

Early in the course of HCV infection of the allograft, histologic findings consist of low-grade lobular inflammation with scattered apoptotic bodies and minimal cell swelling (15). This lesion progresses within 2 to 4 weeks to a more fully developed hepatitis, consisting of portal and lobular inflammation with associated hepatocyte necrosis. Diffuse hepatocyte swelling and zonal swelling around the terminal hepatic venule are frequent. Ductular or ductal damage is milder than in rejection. Lymphoid aggregates and fatty changes represented by midzonal macrovesicular steatosis may be seen. Although epithelioid granulomas have been observed in 10% of explanted livers from HCV-infected recipients, other causes of granulomatous hepatitis, such as CMV, fungal, and mycobacterial infections, drug reactions, and recurrent primary biliary cirrhosis, must be excluded before granulomatous inflammation can be ascribed to HCV (39).

For patients with the severe recurrent fibrosing cholestatic hepatitis variant, liver explants of 8 patients who underwent retransplantation showed bridging fibrosis approaching cirrhosis in two cases, cirrhosis in three, and confluent necrosis with fibrosis in three. Cholestasis was severe, resulting in centrilobular hepatocellular drop-out. Inflammation and piecemeal necrosis were mild in most cases, but lymphoid follicles occasionally were present in portal tract (22).

LONG TERM OUTCOME

The long-term consequences of posttransplantation HCV infection have been studied in patients with up to 10 years of follow-up(8,14-16,20,26, 29,37).

Feray et al found that 61% of 79 patients who underwent liver transplantation for HCV-related disease developed chronic hepatitis. 5-year survivals were 80% and 89%, respectively (8).

Ascher et al also found no differences in patient and graft survival between patients transplanted for chronic hepatitis C and cryptogenic cirrhosis. [7] 3-year survivals were 87% and 73%, respectively. Of the 11 deaths in the HCV group, 2 were related to recurrent disease, and 2 were related to recurrent HCC (37).

Gane et al compared 149 patients who underwent liver transplantation for HCV-related disease with 623 patients who underwent transplantation for other reasons. He found recurrent HCV hepatitis in 88.5% of the HCV-infected group after 35 months of follow-up. [45] Graft loss related to recurrent disease was observed in eight patients (5.4%). 5-year patient survivals were 70% and 69% in HCV and control groups, respectively (16) .

Boker et al analyzed a 10-year outcome of 71 patients with recurrent or acquired HCV infection after liver transplantation, and reported histologic inflammation in 88% and fibrosis in 24% of the patients. [9] Ten-year survivals were 62% and 52%, in HCV and non-HCV groups, respectively. 5-year survivals of HCV patients with and without HCC were 73% to 35%, respectively(20).

In contrast, investigators from Spain examined 81 patients were followed after liver transplantation for hepatitis C. The rate of HCV-related graft cirrhosis was 5 years following OLTx. Overall, patient survival 84% at 5 years, similar to the HCV noncirrhotic pts (86%), but differing from those with graft cirrhosis (54%) (17).

TABLE 1

Investigator	**No. Year follow**	**Recurrent hepatitis**	**Fibrosis**	**Graft survival**	**Patient survival HCV v other**
Feray (1994)	5 year				80% vs 89%
Ascher (1994)	3 year				87% vs 73%
Gane (1996)	35 mo			95%	70% vs 69%
Rosen (1996)	3 year			95%	
Boker (1997)	10 year	88%	24%		62% vs 52%
Prieto (2000)	5 year		28%		86% (54%*) vs 84%

* Patient with HCV graft cirrhosis had a 54% 5 year survival.

In summary, numerous studies of HCV following liver transplantation have shown that disease associated with recurrence may be significant and progressive, but that graft loss and death from recurrence are infrequent in that first decade.

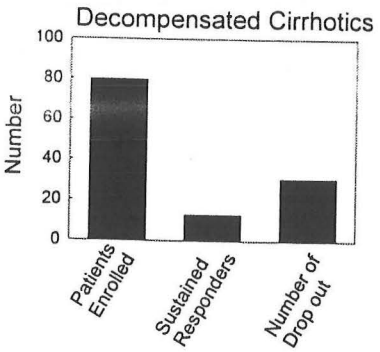
TREATMENT

Treatment of recurrent HCV disease with interferon monotherapy and interferon and ribavirin combination therapy has been examined. No prophylactic therapy is currently available to prevent recurrence of HCV after transplantation. There have been a number of approaches to therapy for recurrent hepatitis C after transplantation, including pre transplant antiviral therapy, early post liver

transplantation antiviral therapy and initiation after the presence of abnormal serum ALT levels and liver histology.

Pre transplant Antiviral Therapy

Preemptive therapy may be initiated while awaiting liver transplantation in order to (1) stabilize and /or improve the hepatic function so that the need for liver transplantation may be delayed and (2) suppress viral replication so that the risk of post transplantation HCV recurrence or aggressive recurrent HCV disease is reduced. Because rapid declines in HCV viral loads are noted as early as the first day of interferon therapy, therapy with interferon before transplantation can theoretically become a way to improving long-term survival of these patients. No studies utilizing interferon or interferon/ribavirin on large groups of transplant candidates have been performed. However, small series has been reported described as treatment of decompensated cirrhotics with a low accelerating dose (LADR) regimen of interferon plus ribavirin. In one study, 80 patients were initiated on the LADR protocol. 64% of the patients had varices and 20% had experienced variceal bleeds, 43% had ascites. The protocol began with 1.5 MU TIW IFN plus 600 mg/day ribavirin. After 2 weeks IFN was increased to 3 MU TIW if the patient was tolerant of therapy and WBC and platelets were stable. Thereafter ribavirn was increased by 200 mg /d every 2 weeks. 17% of the patients had a virological response. 38% of the patients did not complete the trial (40). This study suggests that in specific decompensated cirrhotics, interferon and ribavirin may be used in a careful manner but that dropout rate would be high.



Early post OLTx Antiviral Therapy

There have been 2 studies examining early post transplantation therapy for recurrent hepatitis C :(1) Singh 1998 (n=24) and Sheiner (1998 (n=86). The first study was a controlled, randomized study that began within 2 weeks of transplantation. The patient received interferon 3million units TIW or placebo for 6 months. There was histologic recurrence in 50% vs 42%. There was no difference in survival in the first 1 year. The rejection rate was 50% vs 42% in interferon treated patients versus control (41).

In the second controlled randomized study where therapy was initiated within 2 weeks, 86 recipients were randomized within 2 weeks of transplantation to receive either interferon(n=38) or placebo (n=48) for one year. Patient and graft survival at two years and rate of persistence did not differ between groups. Histologic disease recurrence was observed less frequently in interferon treated patients (8 of 30 evaluable at one year) than in those who were not treated (22 of 41). Therefore, the histologic hepatitis C recurrence rate was 25% vs 53% (42).

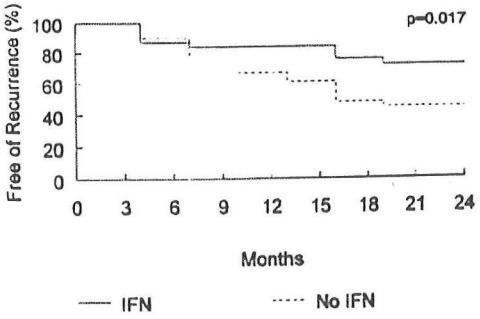


Figure 9

Finally, a recent uncontrolled study demonstrated commencement of interferon early after transplantation, prior to development of disease, is effective in decreasing levels of viremia, without increasing the risk of rejection 65 patients were treated with 1.5 MU of interferon TIW for 3 weeks,

starting 1 week after transplantation, and then increased to 3 MU three times weekly for 52 weeks. Virologic response was observed in 33% of patients at 6 months and in 25% at 1 year (43).

These studies in combination suggest that preemptive therapy post transplantation initiated 2 weeks post transplant may eradicate HCV virus and reduce the recurrence of hepatitis C.

Post Transplant Studies - Late

Interferon Alone

Those studies started later after transplantation do not demonstrate an advantage of anti-viral therapy. One of the earliest studies was performed at UC San Francisco. This study was uncontrolled and the time between transplant and treatment ranged from 4 to 38 months. 18 patients with chronic HCV hepatitis were treated with 3 MU of interferon α TIW for at least 4 months post transplantation. HCV-RNA levels decreased in both responders and nonresponders. However, none of the patients had negative HCV RNA by PCR or a significant improvement in histology(44).

In another study,18 patients with recurrent hepatitis were treated with interferon for 6 months. After cessation of therapy, biochemical response was seen in 28%, consistent with other studies. Long-term sustained response was observed in 73% of the patients who continued interferon beyond 6 months (median 21 months) compared with 43% in those who received just 6 months of treatment. (44).

In a controlled, non randomized study where the mean time between transplant and treatment was 7-60 months, 46 patients with recurrent HCV were treated with interferon for a total of 1-6 months and 32 untreated patients were used as controls. 2 patients (14%) in the study group experienced complete response, but one relapsed after stopping treatment. In contrast to the previous studies, 5/14 (35%) patients developed chronic rejection compared with 1/32 (3%) patients in the untreated group ($P < 0.005$) Histologic improvement was noted in 22% vs 0% control (46).

Another randomized controlled trial of interferon in liver transplant recipients has shown that the rate of response in patients receiving 1, 3, or 6 MU TIW was not significantly different from the rate of response in controls (47).

These studies in combination, would suggest that interferon monotherapy has only a minor role post transplant in eradication of the virus. However, long term effect decreasing the number of patients that decompensate or develop cirrhosis secondary to hepatitis C has not been examined.

Ribavirin

This guanosine analogue is an orally administered antiviral agent with *in vitro* activity against many DNA and RNA viruses. Ribavirin has been examined in recurrent HCV disease (48, 49). In one study, 9 transplant recipients were treated with 800 to 1200 mg ribavirin daily for 3 months (49). Reduction in aminotransferase levels was observed in 5 patients and normalization in 4 by end of treatment. None of the patients cleared virus during treatment, but HCV-RNA levels were reduced in most. Biochemical relapses were observed in all patients, and liver histology did not change.

In another study, ribavirin therapy was initiated at a median 181 days after OLTx in 18 patients with elevated of alanine aminotransferase values and biopsy proven hepatitis and continued for12-44 months. All patient had biochemical responses with normalization in 28% of the patients. Serum HCV RNA levels did not change. Liver biopsies obtained at 17 months (9-38 months) of therapy showed no improvement in necroinflammation. However worsening of fibrosis occurred in12 patients and cirrhosis developed in 5 patient s (28%). Biopsies from 27 untreated patients (median follow up 38 months and 4 patients who received 3months of ribavirin showed cirrhosis in 11and

75%. Therefore, ribavirin did not prevent the development or progression of fibrosis in patients with recurrent hepatitis C (50).

Combination Ribavirin and interferon

In an uncontrolled study, 21 patients with early recurrent HCV infection were treated with the combination of interferon α 3 MU three times a week and oral ribavirin 1000 mg per day for 6 months. After 6 months, patients were maintained on ribavirin alone for another 6 months. Serum ALT levels became normal in all patients after 6 months. HCV RNA (bDNA assay) became undetectable in 10 (48%) patients at the end of treatment. In 5 of 10 responders, HCV RNA reappeared during ribavirin monotherapy. All patients demonstrated initial biochemical response and histologic improvement. None of the patients experienced graft rejection.(51)

In summary, preliminary results show a biochemical response rate in 12% to 28% of liver transplant recipients treated early after transplantation with interferon for 6 months. Prolonged therapy may increase response rates as has been demonstrated in immunocompetent patients. [102] Further studies need to examine whether the prevention of progressive liver disease prior to transplantation can obviate the need for liver transplantation, whether prevention of recurrent infection after transplantation can occur with the administration of agents prior to, at the time and/or following transplantation, whether prevention of the disease can be initiated following transplantation through several interventions such as patient selection or modification of immunosuppression.

Retransplantation

Importantly, the prevalence of HCV infection in patients undergoing liver retransplantation has increased significantly from 6.5% in 1990 to 38.4% in 1995 Although this rising prevalence likely represents the increase in HCV related liver failure as a pimary indication for OLTx and more accurate testing for HCV infection, it does raise concern about the relative contribution of HCV to graft failure (52).

Data have suggested that survival following retransplantation is poor in patients with recurrent HCV. For example, in 27 HCV positive patients undergoing retransplantation, the mortality rate was 67% at 4 months (53). In a French series, there was a diminished 1-2 year graft survival (40%) in the subset of 20 patients who had developed allograft cirrhosis due to recurrent HCV, even when compared with patients retransplanted for hepatitis B related graft failure (54). Analysis of the UNOS data base demonstrated significantly diminished patient survival in the HCV positive group at 5 years vs 61% in the HCV negative group (53). The subgroup of HCV positive patients undergoing retransplantion for causes other than primary nonfuction who had serum bilirubin levels of 10 mg/dL or higher or creatinine concentrations of 2 mg/dL or higher had very poor outcomes. These studies suggest that in many cases, that retransplantation is not an optimal therapeutic option.

KIDNEY TRANSPLANTATION

Ten year survival is 27-67% in adults receiving living related donors. 10 year survival for patients receiving cadaveric donor graft survival has improved from 25% to 56%. For patients alive 10 years after first renal transplantation, 72-95% are alive five years later. For patients who were alive at 10 years, 69% of patients are alive at 20 years after CRT. 8-28% of deaths that occur 10 years after CRT are liver related deaths (LRD) (55).

Patients with chronic liver enzyme elevations or histologic hepatitis at the time of transplantation are at greater risk of liver failure than patients without hepatitis (56-58). HCV is a

major cause of chronic hepatitis post-renal transplantation and as such may contribute to the long-term morbidity and mortality of renal transplant recipients. Natural history data are emerging and are helping to define the consequences of HCV infection following renal transplantation.

HCV Infection in Dialysis Patients

Most of the posttransplant hepatitis C in renal transplant patients is secondary to pretransplant hepatitis C in the recipients. Therefore, the prevalence of HCV in the pretransplant population provides an estimate of the patients at risk for posttransplant hepatitis C. Initially, the EIA2 antibody test was used to assess the prevalence of HCV antibodies in patients with end stage renal disease. Using EIA2, the prevalence of HCV antibodies in patients with end-stage renal disease ranges from 10% to 49% (59-62). These percentages likely under represented the prevalence of HCV in the pretransplant population because anti-HCV is undetectable in a large proportion of patients with chronic renal failure. Therefore, detection of HCV RNA by PCR must be considered the gold standard for the diagnosis of HCV infection in patients with chronic renal failure. HCV RNA was detected in 70-95% of seropositive patients (63,64).

There is no correlation between the presence of viremia, severity of liver histology and elevation of ALT levels. Abnormal liver enzymes are more common in anti-HCV-positive patients on hemodialysis (median 35%) than in those who are seronegative (median 10%) (64-68) However, not infrequently HCV infection also can be demonstrated in dialysis patients with normal ALT(69).

Liver histology is abnormal in most HCV-infected hemodialysis patients. Some degree of chronic hepatitis can be seen in 48 to 100% of patients submitted to liver biopsies (65, 70-71) However, less than 10% of those patients had cirrhosis. Histologic liver injury is poorly reflected by aminotransferase levels. In one study of 16 patients with biopsy-proven chronic hepatitis, only 33% had abnormal ALT (65). In another study of 16 patients, 43% had sustained elevations of ALT, 37% had intermittent elevations of ALT, and 20% had persistently normal ALT(71).

Natural History of Post-Transplant HCV Infection

Hepatitis C disease is most commonly due to progression of infection present before transplantation. Predictors of post-transplantation progression have not been clearly defined, but patients with histologically advanced disease appear to be at risk (72). In patients with pre transplantation infection, the level of virus either increases or remains unchanged after transplantation (73). There is a poor correlation between the level of viremia in the serum and biochemical abnormalities post-transplantation (73, 74). Several studies have assessed the prevalence of liver enzyme elevations in seropositive patients after transplantation (74,75,76,77). Liver test abnormalities after CRT are more common in anti-HCV-positive patients than in those who are anti-HCV-negative. However, elevated ALT levels are observed in fewer than 50% of anti-HCV-positive recipients.

Compilation of Natural History Studies after CRT

In one of the earliest study, (1981) the Massassachusetts General Hospital examined the incidence, etiology and impact of liver disease in renal transplant patients. 405 consecutive CRT were performed between 1970 and 1980. Hepatic dysfunction of at least 2 weeks duration was diagnosed in 42 patients (10.4%). 92.8% of the 28 patients that acquired hepatitis in the first post transplant year developed chronic hepatitis. 64.2% of 14 patients that acquired hepatitis after the first year developed chronic hepatitis. 19/42 (45%)patients died as compared to 16 % of the nonhepatitis patient in the ensuing 36 months. 1 patient died of liver failure while 15/19 died of sepsis. The etiology was identified in 15 patients but not in 27 patients. The authors concluded that the major

cause of liver disease after CRT was an entity known as non A non B hepatitis (HCV) with increased mortality secondary to sepsis (79).

In France, investigators retrospectively studied 499 hepatitis B virus negative patients who receive an initial CRT between 1979 and 1994. 112 anti-HCV positive patients and 387 anti-HCV negative patients were similar, race, sex, age of transplantation. Mean follow up time after transplantation was 79 vs 81 months in each group, respectively. HCV infection after analysis was the only significant factor affecting mortality risk with a risk of 3 times higher in HCV positive recipients than in HCV negative patients. The overall incidence of death was 13.4 vs 4.9% in the anti-HCV positive patients than anti-HCV negative patients, respectively. This study indicates that 5-6 years survival post CRT in the 1980's and early 1990's was lower in anti- HCV positive patients (80).

In a later long term retrospective study from Japan (1973-1996), 80 anti-HCV antibody positive patients were compared to 184 control patients that were HBsAg and HCV antibody negative. The prevalence of the HCV antibody carrier was 28.6%. HCV antibody carriers had a poor survival rate in the second decade compared to the noninfected group 83.7% vs 88.9% for 10 year survival ($p=.44$ and 63.9% vs 87.9% for 20 year survival ($p<0.05$) The poor survival rate was a result of the mortality from liver disorder. As the result of IFNα therapy, 1/8 patients maintained normal biochemic markers and undetectable levels of HCV RNA for 2 years after treatment. The therapy was discontinued in 5 patients with adverse effects of acute rejection, deterioration of diabetes and depression (81). This study suggests that in Japan in the 1970s and 1980's that mortality was higher in HCV positive patients than HCV negative patients in the 2nd decade after transplantation.

In the short term after CRT the clinical course of liver disease is good except in patients with fibrosing cholestatic hepatitis. Most series have shown that patients with HCV infection develop more frequent biochemical liver abnormalities and a more severe pathologic outcome from HCV negative patients (70, 75, 82). Nevertheless, between 20 and 51 % of patients could exhibit normal ALT levels in follow up in spite of the presence of detectable HCV RNA in the serum. Also a healthy carrier state defined as patients with normal ALT levels, an HCV RNA and normal liver biopsy can be seen in around 10% of HCV positive patients (70).

HISTOLOGY

Histologic evidence of hepatitis is more common in anti-HCV-positive transplant recipients with abnormal ALT levels (83). Among anti-HCV-positive recipients with abnormal ALT, 22% to 60% had chronic persistent hepatitis and 20% to 30% had chronic active hepatitis (84). In another study, HBsAg-negative renal transplant recipients who had undergone liver biopsy at or following transplantation were assessed for the prevalence of anti-HCV by EIA1 (83). Chronic active hepatitis was significantly more common in anti-HCV-positive than in anti-HCV-negative patients (61% and 8%, respectively). Although the use of a first-generation anti-HCV assay to define infection likely underestimates the prevalence of HCV, these results support an association between HCV and active histologic disease. Post-transplant liver disease occurred in 64% of anti-HCV- positive recipients vs 18% of anti-HCV-negative recipients ($P < 0.0001$) and survival was 64% in anti-HCV-positive versus 91% in anti-HCV-negative recipients ($P = 0.02$) (74).In another cohort of 399 renal transplant recipients, the prevalence of HCV infection was 29% (85). Sixty-two of the patients with HCV infection underwent liver biopsy and, of those, 42% had chronic active hepatitis and 19% had normal histology; the rest had nonspecific changes. In contrast to the previous series, 5-year graft and patient

survival did not differ between anti-HCV-positive and anti-HCV-negative patients, but those with HCV infection had an increased risk of infectious complications (86).

Another investigator summarized 164 liver biopsies performed in HCV patients shortly after CRT, showing minimal changes, 15% persistent 37% Chronic active 34% Cirrhosis 6% and others 4%. Therefore, chronic hepatitis is common and cirrhosis is infrequentafter CRT (87).

Finally another investigator reported 11/15 HCV RNA positive patients who had sequential biopsies, liver disease progressively worsened and cirrhosis developed in some of them. Many of the patients that developed cirrhosis had received more anti-rejection therapy (88). In 13 patients that had sequential biopsies performed, liver fibrosis worsened (89).

Fibrosing Cholestatic hepatitis

After RT, only a few HCV positive patients with FCHC have been described. One group fo investigators reported that 2/4 patients developed subfulminant liver failure and died 22 and 49 months after transplantation.The third patient suffered hepatic failure and receive a liver transplant. The fourth is awaiting a combined kidney and liver transplant (90).

In summary, HCV infection usually persists after renal transplantation, and the resulting liver disease likely contributes to post renal transplantation morbidity and mortality, particularly in those who have histologic evidence of cirrhosis at the time of transplantation (88).

TREATMENT

The success of interferon treatment in immunocompetent individuals cannot necessarily be extrapolated to transplant recipients who are immunosuppressed. Specific data on the efficacy of interferon in the transplant population is limited, and no controlled trials have been done. Interferon alpha has multiple properties in addition to its antiviral effects. Interferon up-regulates the cell surface expression of class II histocompatibility antigens (HLA) and, therefore, has at least a theoretic risk of precipitating graft rejection, but this remains controversial. In two reports using prophylactic interferon alpha to treat CMV infection in renal transplants, one study found no adverse effect on graft function, but the second noted an increase in graft loss (91, 92). In a recent case report, interferon alpha was given to a renal transplant patient with rapidly progressing HCV-related liver disease and was well tolerated without rejection during the therapy (93).

Not all renal transplant recipients who are seropositive after transplantation will require antiviral therapy. Liver biopsy is important in confirming the diagnosis and in evaluating the severity of disease. Confirmation of the viremic state is needed to verify whether the anti-HCV test is representative of active infection. If the patient is HCV-RNA positive, and has persistently elevated aminotransferases and evidence of moderate to severe chronic hepatitis on biopsy, therapy may be considered.

Interferon

In the early 1990's, these pilot studies showed that, apart from the fact that virological relapse was the rule after withdrawing interferon α , there was an unacceptably high rate of deterioration in renal function. Of 43 evaluable patients from the literature, 46% experience acute renal failure within 3.6 months (range 11 days to 9 months) after initiation of interferon. Of those with acute renal failure, 25% returned to chronic hemodialysis within weeks.

Immunosuppressive therapy may alter the natural history HCV infection following renal transplantation in such a population. Roth has shown that induction therapy significantly increases

the level of HCV RNA (94). Over the long term, after 19 years after grafting, some studies have clearly demonstrated that in HCV positive renal transplant patients, patient survival was significantly lower than that in HCV negative renal transplant patients(94, 95, 80, 81). The major cause of this increase in patient mortality was related to cirrhosis. Likewise at least in one study, graft survival is also significantly lower in HCV positive renal patients that might be due to HCV related renal disease (95).

As indicated in table 2, a number of investigators have attempted to treat patients after CRT (96-99). Acute renal failure during treatment with interferon ranged form 15.4% to 53.6%. Virological response was either not tested or was 0%. Others have demonstrated that allograft function may deteriorate with interferon α therapy. In one study, 6/7 renal transplant recipients and 1/4 recipients of combined liver renal transplant experienced acute deterioration of allograft function associated with IFNα therapy (97).

TABLE 2

Reference	No. of patients	Interferon (MU TIW)	Biochemical--Virological response	Acute renal failure (%)
Thervet E (1994)	13	3 or 5	7.7 – NA	15.4%
Magnone M (1995)	11	1.5-5	N/A – N/A	63.6
Rostaing L (1996)	16	3	77 – 0	37.5%
Ozgur (1995)	5	4.5	60 – N/A	40%

Investigators have also examined the possibility of utilizing interferon prior to transplantation. In the first study, investigators examined interferon therapy for chronic hepatitis C virus infection in uremic patients. 40%(16/39) of the patient did not complete the study, 15/39 (38%) completed the study period had negative HCV RNA end of treatment and 20% had no response. Long term response was not available (101). In a second study, investigators examined the efficacy and toleration of interferon α on HCV infection of hemodialyzed patients. 25% of French hemodialysis patients exhibit the anti HCV antibodies and this is associated with detectable viremia in 85% and results in chronic hepatitis in >90%. 19 anti-HCV antibody positive hemodialyzed patients were given a standard Interferonα. HCV RNA was detectable in 46.7% by PCR and 36.4% by branched chain DNA assay at the end of antiviral therapy, despite biological and histopathological improvement in most. In all but 3 patients, serum HCV RNA reappeared during follow up. (100). The frequency of virological relapse after discontinuation suggests that reinforced therapeutic schedules should be proposed to hemodialyzed patients

Other Therapuetic Options

There are few data in the literature regarding the use of ribavirin in renal transplant patients.

The Lyon group treated seven patients each of whom received 400-800 mg/day for 6 months. During therapy, a biochemical response was observed in four cases, whereas HCV RNA became undetectable during therapy in only two patients (102)

It has been shown that in a small study of 9 patients, aged 52+/- 4 years, grafted 96+/- 15 months, treated with amantadine, that no clearance of HCV RNA occurred but that a decrease in ALT and AST to normal occurred (103).

In summary there is no efficient and safe therapy to treat HCV RNA positive renal transplant patients. The current recommendation appears to be to treat those HCV RNA positive CHD patients who are candidates for a renal transplant before transplantation.

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