Treatment of Hepatitis C in Liver Transplant Patients

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INTRODUCTION

Liver disease caused by the hepatitis C virus (HCV) is the main indication for liver transplantation (OLT) in Europe and the United States. Recurrence of hepatitis C on the graft is a major issue and may lead to graft loss. In the absence of effective prophylaxis, recurrent HCV infection is almost constant. Recurrence of HCV leads to chronic active hepatitis in most patients and may lead to cirrhosis or cholestatic hepatitis in some with a risk of graft failure at medium or long-term. Thus effective treatment for recurrent HCV is mandatory. In this review, current knowledge on the treatment of HCV graft infection after liver transplantation is discussed.

LIVER TRANSPLANTATION FOR HCV-RELATED CIRRHOSIS

The effect of HCV infection on patients and graft survival after liver transplantation is controversial. However, recent data have confirmed that HCV infection impairs patient and allograft survival [1]. HCV recurrence is almost universal and 60-80% of patients will develop lesions of chronic hepatitis on the graft [1-4]. Cholestatic hepatitis can occasionally (2-8%) result in progressive liver dysfunction. Overall, the course of HCV graft disease is accelerated in liver transplant

recipients compared to that observed in immune competent patients, with a 5-year rate of cirrhosis of around 10-20% [1, 3-5] reaching 28-40% [6]. When cirrhosis occurs on the graft, there is a high risk of decompensation in the following years and a 60% risk of death within the year after the first episode of decompensation [7]. At least 10% of patients transplanted for HCV cirrhosis will require retransplantation for hepatitis C graft failure. The factors which influence disease severity and the consequent progression of graft injury or survival remain unclear. Factors clearly associated with the severity of recurrent hepatitis C are: high pre-transplant and early post-transplant serum HCV RNA levels [8, 9], severe early histological recurrence [10], rejection episodes and treatment with more potent immunosuppression (methylprednisone boluses, anti-CD3 monoclonal antibody (OKT3), use of mycofenolate mofetil (MMF) [6, 11-13] and the increasing age of donors [14, 15]. Some of these factors are negative predictors for a virological response to interferon. In the long-term, HCV RNA levels are related to the level of immunosuppression and correlate with the severity of liver injury [16]. Strategies to reduce the impact of immunosuppression on recurrent HCV infection include an overall reduction in immunosuppression, discontinuation of individual agents and the use of immunosuppressive agents with possible antiviral effects. Current data have failed to show differences in the incidence or severity of HCV recurrence using tacrolimus or cyclosporine [3, 8]. Many studies have shown a strong correlation between multiple rejection episodes, exposure to pulse solumedrol, greater daily exposure to steroids or OKT3 and the incidence and severity of HCV recurrence [6, 12, 13, 17]. Despite general acceptance of early steroid withdrawal in patients with chronic hepatitis C, data are limited on the effectiveness of this approach and more recent data suggest that this strategy may have a harmful effect. The post transplantation use of MMF has not been associated with consistent beneficial or deleterious effects [18]. The effects of induction immunosuppression with anti-IL2 receptor antibodies in HCV-infected transplant recipients have not been clearly determined [18].

It therefore appears to be legitimate to offer antiviral therapy to patients with recurrent chronic hepatitis C to stop hepatitis disease progression on the graft. However, certain points should be kept in mind before starting antiviral treatment: (1) 20-30% of patients have a

benign or mild long-term course of HCV hepatitis on the graft and may not require treatment. (2) Optimal treatment is a combination of interferon and ribavirin, which is not well tolerated in transplant patients and which may cause serious side-effects (i.e., hemolytic anemia, risk of rejection). Antiviral therapy could be used: (1) before transplantation to suppress viral replication and reduce the risk of recurrence, (2) early post-transplantation to prevent hepatitis disease progression (3) at time of HCV recurrence.

PRE- AND POST-TRANSPLANTATION TREATMENT OF HCV INFECTION

Pre-transplantation antiviral therapy

Interferon alone or in combination with ribavirin has been shown to reduce viral levels in patients with cirrhosis but its use is very difficult in this setting due to the risk of severe decompensation of cirrhosis and the development of cytopenia or uncontrolled sepsis [19]. Forns et al. evaluated the efficacy and safety of antiviral therapy in 30 patients with HCV cirrhosis awaiting OLT (Child A n=15, Child B/C n=15, genotype 1b n=25) [20]. Treatment with interferon-alpha-2b 3MU/day and ribavirin 800mg/day was initiated when the expected time for OLT was less than 4 months (median duration of treatment 12 weeks). Virological response was observed in 9 patients (30%). After OLT 6 of them (20%) remain free of reinfection after a median follow-up of 46 weeks and HCV infection recurred in 3. A viral load decrease >2 logs at week 4 of treatment was the strongest predictor of virologic response. Side-effects were frequent and dose reduction was necessary in 63% of patients. Everson et al. reported on 102 HCV-cirrhotic patients treated with interferon and ribavirin for one year with a low accelerating dose regimen [21]. The end-of-treatment virological response was 40% and the sustained virological response 20%. None of the 10 sustained responders who underwent OLT had recurrent HCV infection. There are no data on the safety and efficacy of pegylated interferon with or without ribavirin in patients with decompensated HCV cirrhosis. In conclusion, antiviral therapy in patients awaiting OLT should be considered as a strategy to prevent HCV recurrence in patients without severe hepatocellular insufficiency.

Preventive therapy in the early post-transplantation period

HCV RNA is present in the serum of more than 95% of those who are HCV RNA-positive before transplantation, which is the vast majority of patients. HCV RNA is detected in serum as early as the first post-transplant hours [22]. However, HCV RNA is at the lowest level in serum during the first post-transplant week, which is the rationale for starting treatment early [23]. Treatment is generally considered prophylactic if it is started during the 3 first post-transplant weeks. Indeed acute hepatitis on the graft may occur around 3 weeks, with a median at 4 months [4]. Few studies have been performed on prophylactic antiviral treatment. In one study, 86 patients were randomized within 2 weeks after transplantation to receive either interferon alone (n=38) or placebo (n=48) for one year [24]. Patient and graft survival at 2 years and HCV viremia were not affected by treatment, but histological disease recurrence was less frequent in interferon treated patients than in those who were not treated (26% vs. 53%, P=0.01). Interferon and 1-month HCV RNA levels were independent predictors of recurrence. Interferon was stopped in 30% of patients because of adverse effects (acute rejection n=1, thrombopenia n=4, other n=3). In a second trial, 24 patients were randomized 2 weeks after transplantation to receive interferon (n=12) or placebo (n=12) for 6 months [25]. No difference in graft or patient survival, incidence or severity of histological recurrence or 6 months HCV RNA levels were observed. However, interferon significantly delayed the occurrence of HCV hepatitis in treated patients (408 vs. 193 days, P=0.05). Although the use of interferon was not associated with rejection, adverse effects that were probably due to interferon were observed in 50% of the patients (leucopoenia 17%, headache and/or fatigue 33%). In a non-randomized pilot study, 36 patients were treated with interferon-alpha-2b and ribavirin started during the 3 post-transplant weeks [26] and were followed up for a median of 4.5 years. HCV RNA clearance was obtained in 12 patients (33%) at the end of treatment. All these patients remained HCV RNA-negative 6 months after the completion of therapy. Six of the 12 patients who became HCV RNA-negative were infected with genotype 1b (20% response rate), whereas 6 had genotype 2 (100% response rate). Of the remaining 24 patients, only 7 developed recurrent hepatitis with significant fibrosis in 4. Dose reduction because of drug toxicity was needed in 25% of patients but no patients were withdrawn from the

treatment regimen. A subsequent pilot study of combination interferon and ribavirin therapy failed to obtain these excellent results because of high dropout rates (48% related to severe ribavirin-induced hemolysis and interferon-induced neutropenia). Sustained virologic response was achieved in only 16% of patients [27]. Multicenter studies are currently underway and should provide further data on the safety and efficacy of pegylated interferon with or without ribavirin as prophylaxis against recurrent hepatitis C after liver transplantation. In conclusion from the published studies combination therapy is probably more effective on viral load than monotherapy with interferon. The occurrence of hepatitis may be delayed using antiviral therapy. The main drawbacks are the high risk of poor hematological tolerance, the risk of rejection and sepsis. With existing drugs, results in intent to treat are disappointing. Indeed most patients have contraindications to treatment during the first post-transplant weeks.

Treatment of established infection

The treatment of patients with HCV graft reinfection is necessary when the disease is severe to avoid progression of the hepatitis. As in the non-transplant setting, the decision to treat should take into account all parameters: Age, general status, genotype, severity of hepatitis, risk of graft loss, and expected tolerance to treatment. There are some patients that absolutely must be treated: those with fibrosing cholestatic hepatitis due to the poor short-term prognosis and those with rapidly evolving fibrosis on successive biopsies. For the latter reason, we suggest routine yearly biopsies to determine the rate of HCV-related progression of fibrosis.

Interferon or ribavirin monotherapy (Table 1)

Interferon is an immunostimulating agent enhancing the expression of HLA class I and II molecules on hepatocytes and has been reported to facilitate the occurrence of rejection in transplant recipients [28-30]. In our experience, a histological disappearance of interlobular bile duct suggestive of chronic rejection was observed in 5 patients. Three of them were retransplanted [28]. Interferon at doses of 3MU thrice weekly for 6 months had a sustained virologic effect in 0 to 7% of patients and had a minor effect on liver histology [28, 31-33]. Using ribavirin, a biochemical improvement was observed in 44 to 93% of patients but virological clearance in none [32, 34, 35]. The main side-

effect was hemolysis and dosage had to be adapted to renal function since the incidence of hemolysis was significantly associated with higher serum creatinine and decreased creatinine clearance [36].

Author [ref.]	Patients (N)	Treatment (duration)	Interval from transplan -tation (months)	Biochemical response [a] (%)	EOTR (%)	SVR (%)	Histological [a] improvement (%)	Rejection (%)	Cessation of therapy/ side effects (%)
Wright [31]	18	IFN-alpha-2b 3MU x3/week (4 months)	15	28	0	0	0	4	11
Feray [28]	14	IFN-alpha-2b 3MU x3/week (6 months)	44	23	7	7	14	35	28
Cotler [33]	8	IFN-alpha-2a 3MU/day (12 months)	34	14	12.5	12.5	0	12.5	25
Gane [32]	14	IFN-alpha-2b 3MU x3/week (6 months)	6	43	46	NA	21	0	0
Gane [32]	16	RBV (6 months)	7	93	17	NA	64	0	12.5
Gane [34]	7	RBV (6 months)	10	57	0	0	57	0	0
Cattral [35]	9	RBV (6 months)	6	44	0	0	22	0	0

Table 1: Treatment of HCV recurrence: interferon or ribavirin monotherapy.
EOTR = end-of-treatment-response, SVR = sustained virological response, NA = not available, [a] = end of therapy, IFN = interferon, RBV = ribavirin, 3x/week = thrice weekly.

Combination therapy (Table 2)

Combination therapy is more effective than monotherapy with interferon or ribavirin. In a non-randomized pilot study, 21 patients with early recurrent hepatitis (median time from transplantation: 9 months, 3-24) received a combination of interferon and ribavirin for 6 months and then ribavirin alone for an additional 6 months [37]. After 6 months of combination therapy, all patients had normal ALTs and histological improvement. Ten patients (48%) cleared HCV RNA from serum. During maintenance ribavirin monotherapy, ALTs remained normal in all but one patient and HCV RNA reappeared in 5. The main side-effect was anemia, which required cessation of ribavirin therapy in 3 patients. No patient experienced graft rejection. Off-treatment response rates were not reported in this study. In a randomized controlled trial we compared 12 months of combination therapy vs. no treatment in 52 patients with HCV reinfection [38]. Intent to treat analysis for loss of serum HCV RNA showed a sustained virologic response of 21% in the treated group, vs. no patient in the control group (P=0.019). Twelve treated patients (43%) were withdrawn from the study for anemia in 7, chronic rejection in 1, insomnia in 1, depression in 1 and irritability in 2 patients. Lavezzo et al. reported 57 patients treated with interferon and ribavirin for 6 or 12 months [39]. Six additional months of ribavirin monotherapy was given to virologic responders who had tolerated the drug well during combination therapy (n=7). End of treatment and 12 months post-therapy, the sustained virological response was 33 and 22% respectively for 6 months of therapy and 23 and 17% for 12 months of therapy (P=0.4). Genotype non-1 compared to genotype 1 was a significant predictor of sustained virologic response (43% vs. 12% P=0.02) and HCV RNA level below 2meq/mL correlated with a higher rate of end of treatment virologic response. The principal side-effects were anemia and leucopoenia, which required a dose reduction in 51% of patients. Several recent studies of combination therapy have shown that the sustained virological response rate was between 8 to 33% (Table 2) [40-47]. Bizollon et al. described the virological and histological course of 14 liver transplant patients with a sustained virological response to antiviral therapy (combination therapy for 6 months and maintenance ribavirin monotherapy for 12 months) [48].

A complete response was obtained in 93% for 3 years after cessation of therapy and was associated with an absence of detectable intrahepatic HCV RNA and marked histological improvement (marked reduction of necroinflammatory activity, stabilization of the stage of liver fibrosis).

The optimal duration of therapy is uncertain. In contrast to an immunocompetent population, the increase in efficacy seems limited in patients treated for 12 months vs. 6 months [37-39]. The efficacy and duration of additional ribavirin monotherapy in patients with a sustained response to the combination of interferon and ribavirin needs to be determined [49]. As in the non-transplant setting, patients with HCV genotype non-1 responded better than patients with genotype 1 [39]. Other factors such as interval between transplantation to the start of therapy and the type and amount of immunosuppression could influence treatment efficacy.

All these studies showed a high incidence of side-effects compared to that observed in non-transplant patients. Between 20% and 50% of patients could not complete treatment because of side-effects. The most important side-effect of ribavirin is hemolysis, which required dose reductions or cessation of therapy. The use of erythropoietin may be effective in the treatment of anemia during combination therapy. Common side-effects of interferon such as neutropenia, thrombocytopenia or depression are also present. In addition the risk of rejection in patients receiving interferon plus ribavirin seems lower than in patients receiving interferon alone. This may be because ribavirin has an immunosuppressive effect.

There is little information about the potential benefit of pegylated interferon versus interferon. Pegylated interferon is more effective in immunocompetent patients, however its long half-life and its main renal clearance may be a risk in transplant patients. In a randomized-trial 32 liver transplant recipients were treated with pegylated interferon-alpha-2a monotherapy 180µg/week for 48 weeks vs. no treatment [50]. At the end of treatment, 35% of patients had undetectable HCV RNA. Post-treatment data are awaited. Preliminary results of treatment with pegylated interferon and ribavirin showed virological response during treatment in 33% of naive patients and in 18% of non-responders to interferon-alpha-2b and ribavirin patients [51, 52]. We report a sustained virologic response rate of 26% using pegylated interferon-alpha-2b and ribavirin [53]. Recently the group in

Lyon treated 20 patients with increasing doses of pegylated interferon (from 0.5m/kg/week to 1mg/kg by week) plus increasing doses of ribavirin (from 400mg/day to 1000mg/day). 4 patients (20%) were withdrawn from the study and 13 patients required dose reduction of ribavirin because of anemia. The sustained virological response rate was 9/20 (80% of patients were infected with genotype 1).

Authors [ref.]	Patients (N)	Treatment (duration)	Interval from transplan -tation (months)	Biochemical response [a] (%)	EOTR (%)	SVR (%)	Histolo-gical [a] improv-ement (%)	Rejection (%)	Cessation of therapy/ side effects (%)
Bizollon [37]	21	IFN 3MU 3x/week + RBV (6 months) then RBV (6 months)	9	100	48 (6 months) 24 (12 months)	NA	94	0	14
Fischer [40]	8	IFN 3MU 3x/week + RBV (6 months)	5.5	87	12.5	0	NA	0	37.5
Samuel [38]	28	IFN 3MU 3x/week + RBV (12 months)	56	NA	25	21.4	NA	3.5	43
Gopal [41]	12	IFN 3MU 3x/week + RBV (1-17 months)	9	75	50	8.3	NA	8	8
De Vera [44]	32	IFN 1.5-3MU 3x/week + RBV (3-18 months)	NA	77	9	9	0	0	46.8
Alberti [43]	18	IFN 3MU 3x/week + RBV (12 months) then RBV (18-73 months)	9	83	44 (12 months)	33 (18 months)	73	5.5	22.2

Table 2: Treatment of HCV recurrence: interferon plus ribavirin combination therapy.

Ahmad [42]	40	IFN 3-5MU 3x/week (6 months)	24	20	15	2.5	0	0	25
	20	IFN 3-5MU 3x/week + RBV (12 months)	38	25	40	20	0	0	25
Lavezzo [39]	27	IFN 3MU 3x/week + RBV (6 months)[b]	9	66	33	22	52	1.7	2
	30	IFN 3MU 3x/week + RBV (12months)[b]	(3-60)	53	23	17	NA	NA	NA
Menon [45]	26	IFN 3MU 3x/week + RBV (12 months)	14.6	42	35	30.7	75	0	50
Shakil [46]	38	IFN 3MU 3x/week + RBV (12 months) then RBV (6 months)	23	18	13	5	0	0	42
Firpi [47]	54	IFN 3MU 3x/week + RBV (12 months)	31.2	39	38	30	30	5.5	12.9
Dumortier [57]	20	Peglyated IFN 0.5-µg/kg/week + RBV (12 months)	28	75	55	45	NA	25	20

Table 2: (Cont.) Treatment of HCV recurrence: interferon plus ribavirin combination therapy.
EOTR = end-of-treatment-response, SVR = sustained virological response, NA = not available,
[a] = end of therapy, [b] = 6 additional months of ribavirin

Retransplantation

Recurrence of HCV infection may lead to graft failure and an indication for retransplantation in a minority of cases (5-10% of patients). Early reports suggested that the outcome was worse following retransplantation for HCV reinfection than in patients undergoing retransplantation for other indications [54]. However, the natural history of recurrent HCV disease in the second graft seems to be unrelated to that observed in the first graft. Recent studies reported an improved outcome when retransplantation was performed before the development of infectious and renal complications [55, 56]. Due to increased organ shortage and uncertainty regarding the natural history of HCV recurrence, retransplantation is still the subject of debate and requires further studies.

CONCLUSION

Most patients with HCV infection will develop recurrence after transplantation. Although recurrence of HCV on the liver graft does not significantly reduce the medium-term survival of the patient and the graft, HCV infection impairs long-term patient and graft survival. Treatment of recurrent HCV disease with interferon or ribavirin as single agents has been disappointing, but results with combination therapy are encouraging with sustained virologic response in about 25% of patients. Preventive therapy in the early post-transplant period is limited by the high rate of side-effects. Treatment of established infection on the graft is a matter of controversy and several questions should be raised. What is the best treatment? Combination therapy with interferon and ribavirin, or combination pegylated interferon + ribavirin? The duration of therapy and doses are not yet known. The need for ribavirin monotherapy following interferon discontinuation is unclear. Which patients should be treated and what is the optimal timing for initiation of treatment? Further studies are required to resolve these questions. Future research should also focus on improving the tolerance of treatment; this can be achieved with the administration of erythropoietin during ribavirin treatment.

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