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REVIEW ARTICLE

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# Treatment of hepatitis B and C after liver transplantation. Part 2, hepatitis C

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**Abstract** End-stage liver disease caused by the hepatitis C virus is a major indication for liver transplantation. However, recurrence of hepatitis in the graft is a major issue. HCV re-infection after transplantation is almost constant, and recent data confirm that it significantly impairs patient and graft survival. Factors that may influence disease severity and consequent progression of HCV graft injury remain unclear. Chronic HCV infection develops in 60%–80% of patients, and 6%–28% ultimately progress to cirrhosis within 5 years. Pre-transplantation antiviral treatment is not easily related to poor tolerance. Attempts to administer prophylactic post-transplantation antiviral treatment are under evaluation but are limited by antiviral drug side effects. Treatment of established graft lesions with interferon or ribavirin as single agents has been disappointing. Combination therapy gave promising results, with sustained virological response in 25% of patients, but indications, modality and duration of treatment should be assessed.

**Keywords** Hepatitis C · Liver transplantation · Antiviral therapy

## Introduction

Liver disease caused by the hepatitis C virus (HCV) is the main indication for liver transplantation (OLT) in Europe and the USA. Recurrence of hepatitis C in the graft is a major issue and may lead to graft loss. In the absence of effective prophylaxis, recurrent HCV infection is more or less constant. Although the long-term impact of hepatitis C following liver transplantation remains to be determined, recurrence of HCV leads to lobular hepatitis or chronic active hepatitis in most patients and may lead to cirrhosis or cholestatic hepatitis in a minority of them. To date, effective treatment for HCV recurrence is mandatory. Combination therapy with interferon and ribavirin, preferably initiated as soon as possible after transplantation, could have an antiviral effect in 25% of patients. In this review, current knowledge on treatment of HCV graft infection after liver transplantation is discussed.

## Liver transplantation for HCV cirrhosis

The effect of HCV infection on patient and graft survival after liver transplantation is controversial. However, recent data confirm 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 in the graft [1, 2, 3, 4]. Cholestatic hepatitis can occasionally (2%–8%) result in progressive liver dysfunction. Overall, the course of HCV graft disease is more rapid in liver transplant recipients than in immunologically competent patients, with a 5-year cirrhosis rate of around 10%–20% [1, 3, 4, 5] and reaching extremes at 28% [6]. If cirrhosis occurs in the graft there is a high risk of decompensation in the following years and a 60% risk of death within 1 year after the first episode of decompensation [7]. At least 10% of patients who undergo transplantation for HCV cirrhosis

will require retransplantation for hepatitis C graft failure.

Factors that may influence disease severity and 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, OKT3) [6, 11, 12, 13] and increasing age of the donors [14, 15]. Some of these factors are negative predictors for virological response to interferon. In the long term, HCV RNA levels are related to the level of immunosuppression and correlate with severity of liver injury [16]. Strategies for reducing the impact of immunosuppression on recurrent HCV infection include global reduction in immunosuppression, discontinuation of individual agents and 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, OKT3 and 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. Administering mycophenolate mofetil (MMF) after transplantation has not been associated with consistent beneficial or deleterious effects [18]. Effects of induction immunosuppression such as anti-IL2 receptor antibodies in HCV-infected transplant recipients have not been determined definitively [18].

It appears therefore legitimate to offer antiviral therapy to patients who suffer from recurrence of chronic hepatitis C in order to halt disease progression of hepatitis in the graft. However, there are some arguments against antiviral treatment. First, 20%–30% of patients have a benign or mild long-term course of HCV hepatitis in the graft and may not require treatment. Second, optimal treatment is a combination of interferon and ribavirin, which is not well tolerated by transplant patients and may cause serious side effects (i.e. haemolytic anaemia, risk of rejection). The aim of antiviral therapy is to clear HCV, or at least to lower HCV viraemia before or at an early stage after transplantation to reduce disease progression in the graft. Antiviral therapy could be administered (1) before transplantation, to suppress viral replication and reduce the risk of recurrence; (2) early after transplantation, to prevent hepatitis progression; (3) during HCV recurrence.

## Treatment of HCV infection

### Pre-transplantation antiviral therapy

Interferon alone or in combination with ribavirin has been shown to reduce viral levels in cirrhotic patients, but its use is very difficult in this setting, which is related to the risk of severe decompensation of cirrhosis and development of cytopenia or uncontrolled sepsis [19]. Forns et al. assessed 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 α-2b 3 MU/day and ribavirin 800 mg/day was initiated if the expected time until OLT was less than 4 months (median duration of treatment 12 weeks). Virological response was observed in nine patients (30%). After OLT, six patients (20%) remained free of re-infection after a median follow-up time of 46 weeks, and HCV infection recurred in 3 patients. A viral load decrease $>2$ log at week 4 of treatment was the strongest predictor of virological response. Side effects occurred frequently, and dose reduction was necessary in 63% of patients. Everson et al. reported on 102 HCV-cirrhotic patients treated with interferon and ribavirin for 1 year with a low accelerating dose regimen [21]. Virological response at the end of treatment was 40% and sustained virological response 20%. Infection recurred in none of the ten sustained responders who underwent OLT. There are no data on the safety and efficacy of peginterferon 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. Indeed, adverse events are common and sometimes severe.

### Pre-emptive therapy in the early post-transplantation period

HCV RNA is present in the serum of more than 95% of patients who are HCV RNA positive before transplantation. This currently represents the vast majority of patients. HCV RNA is detected within the first post-transplantation hours [22]. However, HCV RNA is at its lowest level in serum during the first post-transplant week; this is why treatment is started early [23]. It is generally considered that the treatment is prophylactic if started during the first three post-transplant weeks. Indeed, acute hepatitis in 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 randomly selected, within 2 weeks of transplantation, to

receive either interferon alone ($n=38$) or placebo ($n=48$) for 1 year [24]. Patient and graft survival after 2 years and HCV viraemia were not affected by the 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 level were independent predictors of recurrence. Interferon was discontinued 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 randomly selected, 2 weeks after transplantation, to receive interferon ($n=12$) or placebo ($n=12$) for 6 months [25]. No differences in graft or patient survival, incidence and severity of histological recurrence or 6 month-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 suspected to be due to interferon were observed in 50% of the patients (leukopenia 17%, headache and/or fatigue 33%). In a non-randomised pilot study, 36 patients were treated with interferon alpha2b and ribavirin after 3 weeks post-transplantation [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 patient remained HCV RNA negative for 6 months after completion of therapy. Of the 12 patients who became HCV RNA negative, six were infected with the genotype 1b (20% response rate), whereas six carried the genotype 2 (100% response rate). Of the remaining 24 patients, only seven developed recurrent hepatitis, with significant fibrosis in four cases. Dose reduction due to drug toxicity was needed in 25% of patients, but no patients were withdrawn from the treatment regimen.

A subsequent pilot study of combined interferon and ribavirin therapy failed to achieve these excellent results because of high dropout rates (48% related to severe ribavirin-induced haemolysis and interferon-induced neutropenia). Sustained virological response was achieved in only 16% of patients [27]. Multicentre studies are currently underway and should provide definitive data on the safety and efficacy of pegylated interferon with or without ribavirin as prophylaxis against recurrent hepatitis C after liver transplantation. Concluding from the published studies, the combination therapy is probably superior to the monotherapy with interferon, at least on the viral load. It seems that the occurrence of hepatitis can be delayed by means of antiviral therapy. The main drawbacks are the high risk of poor haematological tolerance, the risk of rejection and sepsis. With the current drugs, the results are disappointing. Indeed most patients have contraindications to the treatment during the first post-transplant weeks.

## Treatment of established infection

The treatment of patients with HCV graft re-infection is necessary in severe cases 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 the hepatitis, risk of graft loss, and expected tolerance to the treatment. There are some patients for whom treatment is imperative: 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 think that annual routine biopsies are essential to determine the rate of HCV-related fibrosis progression.

## Interferon or ribavirin monotherapy

Studies covering treatment with interferon or ribavirin monotherapy for HCV recurrence is shown in Table 1. Interferon is an immuno-stimulating agent that enhances the expression of HLA class I and II molecules on hepatocytes, which has been reported to facilitate the occurrence of rejection in transplant recipients [28, 29, 30]. In our experience, histological disappearance of interlobular bile duct suggestive of chronic rejection was observed in five patients. Three of them underwent retransplantation [28]. Interferon at doses of 3 MU three times weekly for 6 months had a sustained virological effect in 0%–7% of patients and had a minor histological effect [28, 31, 32, 33]. With the use of 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 haemolysis, and dosage had to be adapted to renal function since the incidence of haemolysis was significantly associated with higher serum creatinine and decreased creatinine clearance [36].

## Combination therapy

Studies covering combination therapy are shown in Table 2. Combination therapy is superior to monotherapy with interferon or ribavirin. In a non-randomised pilot study, 21 patients with early recurrent hepatitis (median time from transplantation 9 months, 3–24 months) 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 ALT levels and showed histological improvement. Ten patients (48%) cleared HCV RNA from their serum. During maintenance ribavirin monotherapy, ALT levels remained normal in all but one patient, and HCV RNA reappeared in five patients. Ribavirin therapy had to be terminated in three

**Table 1** Treatment of HCV recurrence: interferon (*IFN*) or ribavirin monotherapy (*NA* not available)

| Authors [reference no.] | Patients (*n*) | Treatment (duration months) | Interval from transplantation (months) | Biochemical response[a] (%) | End-of-treatment virological response (%) | Sustained virological response (%) | Histological improvement[a] (%) | Rejection (%) | Cessation of therapy/side effects (%) |
|---|---|---|---|---|---|---|---|---|---|
| Wright [31] | 18 | IFN-alpha2b 3 MU thrice weekly (4 months) | 15 | 28 | 0 | 0 | 0 | 4 | 11 |
| Feray [28] | 14 | IFN-alpha2b 3 MU thrice weekly (6 months) | 44 | 23 | 7 | 7 | 14 | 35 | 28 |
| Cotler [33] | 8 | IFN-alpha2a 3 MU daily (12 months) | 34 | 14 | 12.5 | 12.5 | 0 | 12.5 | 25 |
| Gane [32] | 14 | IFN-alpha2b 3 MU thrice weekly (6 months) | 6 | 43 | 46 | NA | 21 | 0 | 0 |
| | 16 | Ribavirin (6 months) | 7 | 93 | 17 | NA | 64 | 0 | 12.5 |
| Gane [34] | 7 | Ribavirin (6 months) | 10 | 57 | 0 | 0 | 57 | 0 | 0 |
| Cattral [35] | 9 | Ribavirin (6 months) | 6 | 44 | 0 | 0 | 22 | 0 | 0 |

[a]End of therapy

patients due to the side-effect anaemia. No patient experienced graft rejection. Off-treatment response rates were not reported in this study.

In a randomised controlled trial we compared a 12-month combination therapy with no treatment at all in 52 HVC-re-infected patients [38]. Analysis for loss of serum HCV RNA showed a sustained virological 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: seven for anaemia, one for chronic rejection, one for insomnia, one for depression, and two for irritability. Lavezzo et al. reported 57 patients treated with interferon and ribavirin for 6 and 12 months [39]. Six additional months of ribavirin monotherapy were administered to virological responders who had tolerated the drug well during combination therapy ($n=7$). End-of-treatment and 12 month post-therapy 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 virological response (43% vs 12%, $P=0.02$), and HCV RNA levels below 2 Meq/ml correlated with a higher rate of end-of-treatment virological response. The principal side effects were anaemia and leukopenia, which required dose reduction in 51% of the patients.

Several recent studies of combination therapy have shown that the sustained virological response rate was between 8% and 33% (Table 2) [40, 41, 42, 43, 44, 45, 46, 47]. Bizollon et al. described the virological and histological course of 14 liver transplant patients with sustained virological response to antiviral therapy (combination therapy for 6 months and maintenance ribavirin monotherapy for 12 months) [48]. A complete response was sustained in 93% for 3 years after cessation of therapy and associated with absence of detectable intrahepatic HCV RNA and marked histological improvement. Absence of detectable graft HCV RNA at the end of treatment seems to be a reliable indicator of sustained virological response.

The optimal duration of therapy is uncertain. In contrast to the immunocompetent population, the increase in efficacy seemed limited in patients treated for 12 months compared with those treated for 6 months [37, 38, 39]. The efficacy and duration of additional ribavirin monotherapy in patients with sustained response to interferon and ribavirin combination should be determined [49]. As in non-transplant settings, patients with HCV genotype non-1 responded better than patients with genotype 1 [39]. Other factors, such as the time interval from transplantation to the start of therapy and the type and amount of immunosuppression, could influence the efficacy of therapy.

All these studies showed a higher incidence of side effects than in non-transplant patients. Between 20% and 50% of patients were unable to complete treatment

**Table 2** Treatment of HCV recurrence: interferon (*IFN*) plus ribavirin combination therapy (*NA* not available)

| Authors [reference no.] | Patients (*n*) | Treatment (duration months) | Interval from transplantation (months) | Biochemical response[a] (%) | End-of-treatment virological response (%) | Sustained virological response (%) | Histological improvement[a] (%) | Rejection (%) | Cessation of therapy due to side effects (%) |
|---|---|---|---|---|---|---|---|---|---|
| Bizollon [37] | 21 | IFN 3 MU thrice weekly + ribavirin (6 months) then ribavirin (6 months) | 9 | 100 | 48 (6 months) 24 (12 months) | NA | 94 | 0 | 14 |
| Fischer [40] | 8 | IFN 3 MU thrice weekly + ribavirin (6 months) | 5.5 | 87 | 12.5 | 0 | NA | 0 | 37.5 |
| Samuel [38] | 28 | IFN 3 MU thrice weekly + ribavirin (12 months) | 56 | NA | 25 | 21.4 | NA | 3.5 | 43 |
| Gopal [41] | 12 | IFN 3 MU thrice weekly + ribavirin (1–17 months) | 9 | 75 | 50 | 8.3 | NA | 8 | 8 |
| De Vera [44] | 32 | IFN 1.5–3 MU thrice weekly + ribavirin (3–18 months) | NA | 77 | 9 | 9 | 0 | 0 | 46.8 |
| Alberti [43] | 18 | IFN 3 MU thrice weekly + ribavirin (12 months) then ribavirin (18–73 months) | 9 | 83 | 44 (12 months) | 33 (18 months) | 73 | 5.5 | 22.2 |
| Ahmad [42] | 40 | IFN 3–5 MU thrice weekly (6 months) | 24 | 20 | 15 | 2.5 | 0 | 0 | 25 |
| | 20 | IFN 3–5 MU thrice weekly + ribavirin (12 months) | 38 | 25 | 40 | 20 | 0 | 0 | 25 |
| Lavezzo [39] | 27 | IFN 3 MU thrice weekly + ribavirin (6 months)[b] | 9 | 66 | 33 | 22 | 52 | 1.7 | 2 |
| | 30 | IFN 3 MU thrice weekly + ribavirin (12 months)[b] | (3–60) | 53 | 23 | 17 | | | |
| Menon [45] | 26 | IFN 3 MU thrice weekly + ribavirin (12 months) | 14.6 | 42 | 35 | 30.7 | 75 | 0 | 50 |
| Shakil [46] | 38 | IFN 3 MU thrice weekly + ribavirin (12 months) then ribavirin (6 months) | 23 | 18 | 13 | 5 | 0 | 0 | 42 |
| Firpi [47] | 54 | IFN 3 MU thrice weekly + ribavirin (12 months) | 31.2 | 39 | 38 | 30 | 30 | 5.5 | 12.9 |

[a]End of therapy
[b]Six additional months of ribavirin monotherapy was given to virologic responders who had well tolerated the drug during combination therapy

because of drug side effects. The most significant side effect of ribavirin was haemolysis, which entailed dose reduction or cessation of therapy. Erythropoietin may be effective in the treatment of anaemia during combination therapy. Common side effects of interferon, such as neutropenia, thrombocytopenia or depression, are more frequent in the transplant setting. In addition, the risk of rejection in patients receiving interferon plus ribavirin seems lower than in those receiving interferon alone. This may be due to an immunosuppressive effect of ribavirin.

We have no information on the potential benefit of pegylated interferon versus interferon. Pegylated interferon is more effective in immunocompetent patients; however, its long half-life and its renal clearance may be a risk for transplant patients. In a randomised trial, 32 liver transplant recipients were treated with pegylated interferon α-2a 180 μg/week for 48 weeks and compared with untreated patients [50]. At the end of treatment, 35% of patients had undetectable HCV RNA. Post-treatment data are pending. Preliminary results of combination treatment with pegylated interferon and ribavirin showed a virological response in 33% of naïve patients and 18% of patients previously treated with interferon α-2b and ribavirin [51, 52].

We report a sustained virological response rate of 26% to pegylated interferon α-2b and ribavirin [53]. Treatment with interferon plus ribavirin and amantadine has yet to be assessed.

### Retransplantation

Recurrence of HCV infection may lead to graft failure and indicates retransplantation in a minority of cases (5%–10% of patients). Early reports suggested a less favourable outcome in patients who underwent retransplantation for HCV re-infection than in patients who underwent retransplantation for other indications [54]. However, the development of recurrent HCV disease in the second graft seems to be unrelated to that observed in the first. Recent studies report an improved outcome if patients undergo retransplantation before infections and renal complications develop [55, 56]. Due to increased organ shortage and uncertainty regarding the natural history of HCV recurrence, retransplantation is still the subject of debate and needs to be further studied.

### Conclusion

Most patients with HCV infection will develop recurrence after undergoing transplantation. Although recurrence of HCV in the liver graft does not significantly reduce the medium-term survival rate of patient and 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 the results of combination therapy are encouraging, with a sustained virological response in about 25% of patients. Pre-emptive therapy in the early post-transplant period is limited by the high rate of side effects. Treatment of established infection in the graft is a matter of controversy, and several questions have yet to be answered. What is the best treatment? Combination therapy with interferon and ribavirin; pegylated interferon vs interferon? Duration of therapy and doses is yet unknown. The need for ribavirin monotherapy following interferon discontinuation is unclear. Which patients should be treated? When should treatment optimally begin? Further studies are required to resolve these questions. Future research should also focus on improving the tolerance of treatment.

## Liver transplantation in patients with HIV infection co-infected with HCV

The prognosis of infection due to human immunodeficiency virus (HIV) has been dramatically improved over the past years since the advent of highly active antiretroviral therapy (HAART). However, 20%–40% of HIV-infected patients are co-infected with HCV or HBV. The outcome of viral hepatitis in HIV co-infected patients is more rapid and severe. For these reasons there is a strong demand for OLT for HIV-infected patients with life-threatening viral liver disease. Before the advent of HAART, results of OLT in HIV-infected patients were poor [57]. With the advent of HAART and the improvement of the HIV infection, the issue of OLT has been raised in patients with viral liver disease. However, many issues are yet to be resolved: the ideal timing for OLT, the risk of HIV transmission to healthcare workers, the problem of drug interactions between calcineurin inhibitors and HAART, mitochondria toxicity of HAART and the risk of progression of HIV infection after transplantation [58]. Liver transplantation in HIV–HCV co-infected patients represents the most difficult and most important issue. The outcome of such co-infected patients after liver transplantation is still mostly unknown [58, 59, 60]. It appears that OLT is feasible; however, the main problem is the severity of HCV recurrence and the toxicity of HAART alone and in combination with ribavirin.

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