

Managing hepatitis C in liver transplant patients with recurrent infection

Tim Zimmermann¹
Gerd Otto²
Marcus Schuchmann¹

¹Department of Internal Medicine,
²Transplantation Surgery, University
of Mainz, Germany

Abstract: Hepatitis C virus (HCV) reinfection after liver transplantation (LT) and recurrent hepatitis C often lead to recurrent cirrhosis (RC). RC is one of the most frequent complications resulting in organ failure and early death after LT in HCV-positive patients with reported 5-year rates from 20% to 40%. As HCV-cirrhosis is one of the leading indications for LT, the therapeutic management is a central issue. To date, the best available therapy is a combination of pegylated interferon + ribavirin in patients with established recurrent hepatitis C proven by liver biopsy. Although increasing experience in using interferon therapy after LT has suggested better response rates, treatment is limited by a poor tolerability and high rates of severe side effects, necessitating lower doses or withdrawal of therapy. The extent to which dose reductions and the concomitant administration of growth factors affect virological response or prevent complications is still to be determined. Prospective clinical trials are mandatory to identify the best time point and schedule of antiviral treatment in transplant patients. Currently, therapeutic options need to be discussed for each individual patient. Therefore therapy should be carried out only in transplant centers with experience in managing hepatitis C after LT.

Keywords: hepatitis C, liver transplantation, recurrent infection, treatment

Introduction to hepatitis C virus management in liver transplant patients and implications for graft survival

Nearly 300 million people worldwide are chronically infected with the hepatitis C virus (HCV) and 20% to 30% develop liver cirrhosis within 20 to 30 years. HCV-related end-stage cirrhosis is currently the leading indication for liver transplantation (LT).^{1,2} Unfortunately, LT does not cure the infection and HCV reinfection of the liver allograft occurs almost universally after LT.³⁻⁵ Liver allografts become infected during reperfusion in the operating room, and viral titers reach pretransplant levels within 72 hours.⁶ HCV recurrence is favored by potent immunosuppression regimens.^{7,8}

Once reinfection is established the severity of recurrent hepatitis C ranges from minimal to severe liver damage and can progress to clinical decompensation, graft loss, and subsequent death.^{9,10,11}

Reinfected HCV positive patients show a lower 5-year survival after transplantation compared to HCV negative patients.^{12,13} The reason for the significantly worse survival in HCV-reinfected patients is recurrent cirrhosis (RC).¹⁴ The course of RC is accelerated in transplant recipients compared with immunocompetent patients, with reported 5-year rates of RC up to 28% compared with less than 5% in nontransplant patients.^{15,16} In liver

Correspondence: Marcus Schuchmann
Department of Internal Medicine,
Johannes Gutenberg University of Mainz,
Langenbeck Str. 1, 55101 Mainz, Germany
Tel +49 6131 177389
Fax +49 6131 173435
Email schuchm@uni-mainz.de

transplant recipients, the 5-year risk for decompensation is 18%.¹⁷ RC occurs especially in patients infected with HCV genotype 1, which is the most common genotype in North America and Europe.

Clinical courses of hepatitis C after LT

The clinical course of HCV recurrence is highly variable and ranges from normal or near-normal serum aminotransferases with minimal inflammation on liver biopsy to rapidly progressive, cholestatic hepatitis with rapid fibrosis leading to RC and graft failure sometimes within the first year after LT.^{5,9} Fibrosing cholestatic hepatitis C is an uncommon but well-documented complication in liver transplantation, which occurs in 5% to 10% of patients 1 to 3 months after LT. Variables leading to this enormous range of severity of disease recurrence are not well understood. While most published data point to risk factors for fibrosis progression after LT, to date no predictive factors are known to identify patients at high risk for rapid RC. Early markers may include hepatic stellate cell activation and a hepatic venous pressure gradient of 6 mmHg.^{18,19}

Diagnosis of recurrent hepatitis C

Recurrent hepatitis C after LT may be difficult to diagnose clinically and may be confused with acute cellular rejection in the graft. Serum alanine aminotransferase (ALT) levels are often elevated. Diagnosis is based on HCV-RNA levels and liver biopsy to confirm the diagnosis, stage the disease (inflammation, fibrosis), and determine treatment.²⁰ Even in a given biopsy, differentiation between rejection with hepatitis C and hepatitis C alone can be very difficult and clinical features must also be considered (eg, the degree of immunosuppression, previous rejection).

Risk factors

Immunopathogenesis of HCV and recurrent hepatitis C

The specific CD4+ and CD8+ T cell responses to HCV appear to be important determinants of viral clearance during acute HCV infection and of the severity of histologic recurrence following liver transplantation.^{21,22} Patients with severe recurrence failed to develop immunoreactivity to HCV antigens.

Although virus-specific CD4+ and CD8+ T cells and antibody responses are induced in the first weeks of acute hepatitis C, patients with chronic viral persistence go through a phase of incomplete viral control accompanied by a decline in HCV-specific CD4+ T cell responses. In contrast,

patients with self-limited acute hepatitis C maintained strong CD4+ T cells for many years following resolution of disease.²³ Lucas et al have shown that loss of function, ie, secretion of IFN- γ and proliferation, preceded the physical deletion of HCV-specific CD4+ T cells.²⁴

Specific HCV T cell responses can be detected as early as 6 weeks to 3 months after LT.^{25,26} Strong CD4+ T cell responses have been reported to be associated with improved outcomes with less severe injury at 12 months post-transplant.²⁶ Although HCV-specific T cell responses have been demonstrated, the degree to which these responses mediate hepatocellular injury remains unclear, given the high rates of major histocompatibility complex (MHC) mismatching in LT.^{27,28} Donor MHC-restricted HCV-specific T cell responses have been reported after LT, but the extent to which they contribute to HCV pathogenesis in this setting remains unclear.²⁹ Although HCV-specific antiviral responses may not correlate with histological outcome, it is possible that the frequency or function of CD4+ regulatory T cells may correlate with outcomes. Thus, the degree of regulation of inflammatory responses may play a role in the development of liver damage post-transplantation. Injury at the time of recurrent hepatitis is characterized by an activation of hepatic stellate cells (HSC), which has been shown to be associated with worse outcome at 12 months, with more fibrosis in patients who had early HSC activation at 4 months during acute recurrent hepatitis.^{18,30} In the first 6 months after LT higher viral loads seem to drive an enhanced proliferative, proapoptotic and profibrotic host response.

Recent advances in the field of HCV immunopathogenesis have expanded the understanding of immunoregulatory receptors on T cells, most notably the programmed death receptor 1 (PD-1) in the nontransplant setting, which has been described as a major mediator of CD8+ T cell exhaustion.³¹ In patients who achieved spontaneous viral clearance, PD-1 expression tended to decline or to disappear on virus-specific CD8+ T-cells, whereas in patients who developed chronic infection, PD-1 expression persisted at high levels. A correlation was established between the strength of PD-1 expression and viral load.³² PD-1 blockade was shown to restore HCV-specific CD4+ T cell function and proliferation.³³ In vitro studies using antigen-specific stimulation in the presence of PD-1 antibodies or antibodies against the ligand PD-L1 and PD-L2 led to restoration of IFN- γ production by virus-specific CD8+ T cells. A recent study found that intrahepatic HCV-specific CD8+ T cells from chronically HCV-infected patients were highly PD-1 positive, profoundly dysfunctional, and unexpectedly

refractory to PD-1/PD-L blockade, in contrast to circulating PD-1-intermediate HCV-specific CD8+ T cells with responsiveness to PD-1/PD-L blockade.³⁴ This intrahepatic functional impairment was HCV-specific and directly associated with the level of PD-1 expression. Therefore, the responsiveness to PD-1/PD-L blockade seems to depend on the compartmentalization (liver–peripheral blood).

These observations could offer new opportunities to manipulate virus-specific immune responses *in vivo*. To date, no data exist on the role of PD-1 in recurrent hepatitis C after LT.

Clinical risk factors

A number of clinical risk factors for patients with recurrent hepatitis C have been reported:

The strongest predictor of outcome is donor age. In contrast to non-HCV infected patients, who show no survival disadvantage with grafts from donors aged 60 to 80 years, HCV recurrence is more severe when older donors are used.^{14,35–39}

The influence of human leukocyte antigen mismatches on the severity of disease recurrence following LT remains controversial.^{40,41} No sites of mismatches associated with disease recurrence have been identified.

The type of donor used may affect patient and graft survival. More severe HCV-recurrence was reported in patients who underwent adult-to-adult living donor liver transplantation, whereas larger studies did not confirm this finding.^{42–50} A multicenter living donor liver transplant cohort revealed that the experience of the transplant center may be the driving factor in predicting patient outcomes.⁵¹ Patient and graft survival did not differ among recipients of living or deceased organs in centers that had performed at least 20 living donor transplants.

The influence of HCV genotype on the severity of disease recurrence in genotype 1 and non-1 patients following LT is controversial, too.^{40,41,52–55}

The degree of divergence of HCV quasispecies seems to be enhanced in patients with severe recurrent hepatitis C.⁵⁶

Within 72 hours after LT, serum HCV-RNA levels increase from 4- to 100-fold.⁵⁷ A relationship between pretransplant viral load and viral load after LT on graft and patient survival seems possible. Whether the pretransplant HCV viral load influences the severity of HCV recurrence is discussed.^{52,54,58} A high viral load correlates with severe hepatitis C recurrence and is associated with an activation of inflammatory, profibrotic, and proapoptotic pathways, whereas the grade of inflammation in the native liver at the

time of LT and the time of recurrence are not predictive for progression of hepatitis C after LT.^{59–61}

In summary high titers of HCV-RNA in the explanted liver as well as after LT may be risk factors for increased histological activity and fibrosis.^{57,62,63}

Since viral and immunological activity are closely linked to each other, the level and type of immunosuppression and treatment of acute rejections after LT influence the severity of disease recurrence.^{54,64,65}

Immunosuppression

Immunosuppression is one of the major factors that accelerate the course of HCV recurrence. High-dose bolus steroids, rapid steroid tapering, and monoclonal antibody preparations such as OKT3 to treat acute rejection affect the progression of recurrent hepatitis C and should be avoided if possible.^{39,54,64–70}

Although some studies have reported antiviral effects of cyclosporine and a shorter time of HCV recurrence after LT when using tacrolimus, there are no prospective, randomized controlled trials showing differences between cyclosporin and tacrolimus in their effect on HCV recurrence.^{69,71–73} In one prospective study there was no difference between calcineurin inhibitors during the first year after LT, although the time to acute hepatitis was significantly shorter in the tacrolimus group.⁶⁸

Use of mycophenolate mofetil (MMF) has been debated: although MMF in combination with tacrolimus and steroids was associated with improved long-term patient and graft survival and lower rates of acute rejection, MMF did not show significant histological benefit on HCV recurrence.^{8,74}

To date there are no convincing data to support the use of any specific induction or maintenance regimen.

A meta-analysis and meta-regression of 30 publications representing 19 randomized trials that compared steroid-free with steroid-based immunosuppression, showed that HCV recurrence was lower with steroid avoidance.⁷⁵ In studies in which steroids were replaced by other immunosuppressive agents, the risks of diabetes and rejection were markedly lower in steroid-free arms. In studies in which steroids were not replaced, rejection rates were higher in steroid-free arms.⁷⁵ In a prospective, randomized trial of 198 LT patients treated with basiliximab and cyclosporine, either in combination with prednisone or without prednisone, immunosuppression without steroids in HCV patients was safe with a lower rate of bacterial infections and metabolic complications.⁷⁶ Histological short-term evolution of HCV recurrence was favorable, with lower fibrosis scores compared with the

steroid group, whereas another study found no impact on hepatic fibrosis progression.^{76,77} In conclusion, avoiding steroids by induction with interleukin-2 receptor antibodies (ie, basiliximab) seems to be safe while eliminating some of the negative consequences and side effects associated with steroids.⁷⁸

Therapy

In terms of severity of recurrent hepatitis C, it seems reasonable to treat hepatitis C after liver transplantation, particularly since rates of sustained virological response (SVR) with pegylated interferon and ribavirin in the HCV-infected nontransplanted population are acceptable.⁷⁹ However, patients with HCV reinfection of the graft usually have higher viral loads and harbor genotype 1 more prevalently than immunocompetent patients; both factors are predictive for a lower virological response rate.⁸⁰⁻⁸³ Moreover, many patients had been treated before transplantation with previous treatment failure and relapse.

Antiviral therapy has been occasionally associated with severe rejection of the graft and the general condition of many patients prevents the option of treatment, eg, due to infectious postoperative complications, anemia, and renal failure.⁸⁴⁻⁸⁶ The optimal time for treatment start, dosage, and duration after LT are still undefined. Different immunosuppressive regimens, induction therapies, use of steroids, dose reduction protocols, and antiviral therapeutic strategies are still debated.

Published data on the effect of treatment regimens on recurrent hepatitis C and RC progression are difficult to interpret, the results varying according to genotype, selection processes, inclusion criteria, and pretreatment strategies. Remarkable differences in SVR rates between 14% and 50% are reported (Figure 1). The available therapies do not solve the clinical problems of RC since there is only evidence for survival benefit in patients who show a virological response.^{87,88}

Nevertheless, management of chronic hepatitis C in LT recipients with recurrent hepatitis C has improved significantly during the past decade.⁸⁸⁻¹¹¹ The best results were obtained with pegylated interferon (PEG-IFN) alpha in combination with ribavirin, with higher SVR rates compared to IFN or ribavirin monotherapies.⁹³

One of the main problems is to find the individual balance between tolerable and manageable side effects and maintain therapy over the whole time of treatment to maximize the number of SVR and minimize the number of relapsers.

Strategies to prevent HCV-recurrent cirrhosis and manage hepatitis C after LT are reviewed and discussed below.

Overview of available agents to manage infection

Strategies for managing HCV recurrence can be separated into pre-, peri-, and post-LT periods. Figure 2 presents an overview of the different timepoints and options for therapeutic intervention.

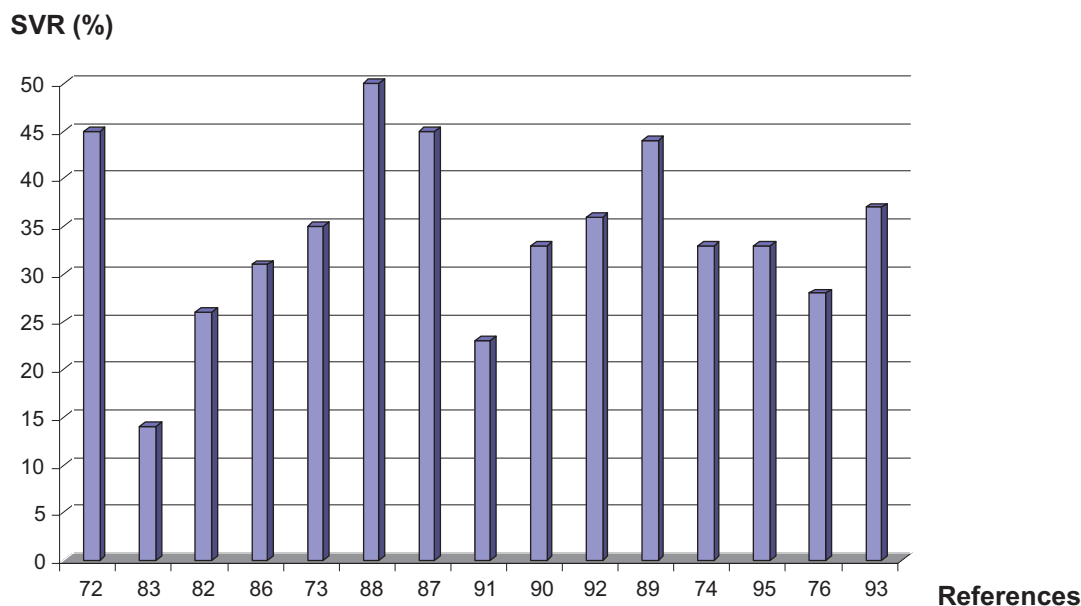


Figure 1 Sustained virological response (SVR) rates in studies with pegylated IFN α and ribavirin after diagnosis of recurrent hepatitis C.

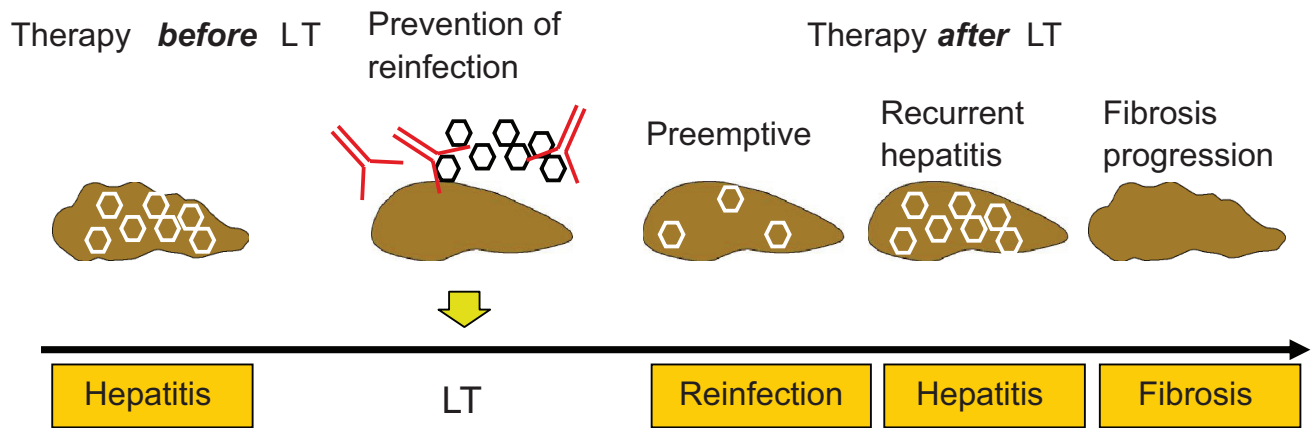


Figure 2 Treatment strategies.
Abbreviation: LT, liver transplantation.

Therapy before LT

The aim of this strategy is to render patients free of HCV-RNA before going into LT. Guidelines for the treatment of adult patients with hepatitis C in the nontransplant setting were published by the American Association for the Study of Liver Diseases (AASLD) and were recently updated.^{112,113} Treatment duration and dosage depends on the genotype and the virological response. Patients with genotype 1 are treated with PEG-IFN + ribavirin (1000 mg/day \leq 75 kg; 1200 mg/day $>$ 75 kg). When there is a complete early virological response (EVR), as indicated by negative HCV-RNA at week 12, the treatment is continued for a total of 48 weeks. In case of a partial EVR (HCV-RNA declines $>$ 2 log) HCV-RNA is determined at week 24; if negative, treatment is continued for 48 weeks, if positive, treatment will be discontinued. If there is no EVR (HCV-RNA $\downarrow \leq$ 2 log) at week 12, treatment is stopped.

In genotype 2 or 3 patients treatment is carried out with PEG-IFN + ribavirin (800 mg/day) for 24 weeks.

Recent data in the non-transplant setting suggest, that in patients with pretreatment low viral load ($<$ 800,000 IU/mL) and rapid virological response (RVR) duration of therapy can be reduced.¹¹⁴

Eradication of HCV infection prior to transplantation would be the ideal approach as patients who undergo transplantation in the absence of viremia are much less likely to have recurrent infection. However, treatment of patients with cirrhosis on the waiting list is very difficult and can be dangerous in the setting of decompensated liver function, exacerbation of encephalopathy, infections (spontaneous bacterial peritonitis), thrombocytopenia with bleedings, and other serious complications. Previous studies showed low rates of viral clearance.^{115,116} Everson et al

treated 124 patients with advanced HCV cirrhosis with PEG-IFN + ribavirin with an overall SVR of 22%. Genotype was an important determinant of response (SVR rate of 60% among patients with genotype 2 or 3 and 11% among patients with genotype 1).¹¹⁷ To date there is no consensus about dosing and optimal treatment regimen. Dose reductions are frequent due to low blood count levels and renal failure.

The lower tolerability in patients with decompensated cirrhosis on the waiting list and the elevated risk of severe side effects in this patient group limit therapeutical options. Therefore, according to International Liver Transplantation Society Consensus Panel, treatment is not advised for patients with a Child-Turcotte-Pugh (CTP) score of \geq 11 or a model for end-stage liver disease (MELD) score of \geq 25.¹¹⁸

Perioperative therapy (hepatitis C immunoglobulin)

Unlike hepatitis B, no effective immunoglobulin prophylaxis exists for hepatitis C. Studies evaluating HCV-specific immunoglobulins in vivo have produced inconclusive results. An initial report demonstrated that anti-HCV containing hepatitis B immunoglobulin reduced HCV reinfection in HBV/HCV co-infected liver transplant patients.¹¹⁹ However, a randomized, controlled trial of hepatitis C immunoglobulin to prevent recurrent hepatitis C did not find any substantial benefit.¹²⁰ One possible explanation is that nonneutralizing antibodies contained in the polyclonal preparations may interfere with the function of neutralizing antibodies.¹²¹ To date different experimental immunoglobulin preparations are in various stages of testing. Further studies are necessary and underway.^{120,122}

Therapy after LT

Preemptive therapy

After LT two treatment strategies have been tried: preemptive antiviral therapy soon after LT, and treatment of patients after histological evidence of recurrent HCV (Figure 2). The aim of a preemptive therapy is to render patients' HCV viral load negative or to minimize recurrent hepatitis C. Interferon-based regimens have been tested, as interferon monotherapy^{123–125} or a combination of interferon and ribavirin,¹²⁶ peginterferon alone¹²⁷ or in combination with ribavirin.^{128,129} Although PEG-IFN alpha-2a¹²⁷ or -2b¹²⁸ plus ribavirin were safe and well tolerated, the efficacy was very low, with SVR rates of 8%¹²⁷ and 18%.¹²⁸

Preemptive therapy is initiated within 2 to 6 weeks after transplantation. During this time tolerability of therapy, particularly ribavirin, is often low and anemia leads to dose reductions or discontinuations of ribavirin.¹³⁰ In one study only 35% (44/124) of transplant recipients were able to initiate prophylactic therapy.¹²⁸ Reasons for ineligibility included anemia, acute rejection, infectious complications, renal failure, and myocardial infarction. Many patients are in the early post-transplant period simply “too sick” to tolerate therapy, resulting in very low SVR rates. The decision to treat is made on a patient by patient basis.

In summary, preemptive therapy and prophylactic treatment of patients transplanted for HCV-related cirrhosis are not generally recommended. The only current indications for preemptive therapy today are in retransplanted patients for rapidly progressive recurrent HCV and HCV-negative transplant recipients who receive allografts from HCV-positive donors.¹¹⁸

Therapy of recurrent hepatitis C

Treatment is initiated if recurrent hepatitis C is associated with significant liver injury as proven by biopsy (Desmet fibrosis score ≥ 2). In the past decade many studies have been published dealing with this topic, but there are only very few prospective randomized studies.^{131,132} Most studies have been single-center trials with small numbers of patients with varying numbers of genotype 1/non-1 and different proportions of previous nonresponders.

In addition, to reduce the immunosuppressive regimens, specific treatment for HCV recurrence is based on interferon, ribavirin, and combination therapy.

Interferon monotherapy

Trials with interferon monotherapy showed little efficacy.^{84,133–135} Patients showed no significant improvement in histology.

Even with PEG-IFN, SVR rates were low (12%), although patients had significantly lower HCV-RNA levels compared with untreated controls.¹²⁷

Ribavirin monotherapy

Ribavirin monotherapy demonstrated poor efficacy without virological response.^{136,137} The necessity for dose reductions after LT due to poor tolerability related to calcineurin inhibitor-induced reduced glomerular filtration rate may contribute to its decreased efficacy. Since ribavirin monotherapy lacks efficacy even in the nontransplant setting, monotherapy has been abandoned.

Standard interferon plus ribavirin

Combination therapy with standard IFN and ribavirin resulted in SVR rates of over 20% in some studies, but up to 50% of patients drop out due to side effects, mainly anemia.^{91–93,98,127,138–144}

PEG-IFN plus ribavirin

Best treatment responses were obtained with the combination of PEG-IFN and ribavirin.^{93–96,98,99,102,105,106,109,110,127,145,146}

Most published studies are uncontrolled trials with a high variability in patient selection, and type and timing of antiviral therapy. Rates of SVR have been less than those achieved in the nontransplant setting. Reasons were a higher viral load after LT, a higher frequency of genotype 1 patients, poor tolerability of treatment after LT, and need for frequent dose reductions. The current SVR rate with this regimen is 30%, ranging from 12% to 43% in small studies.^{93–96,100,101,104,105} A meta-analysis from over 40 treatment trials estimated that SVR rates of combination therapy were 24% and 27%.¹⁴⁷ A recent systematic review of predominantly therapeutic intervention studies by Berenguer et al confirmed that 30.2% of patients treated with PEG-IFN plus ribavirin will attain SVR.¹³¹ Dose reductions and discontinuation of treatment were common in these studies: 73% and 27.6%, respectively.

Fibrosis progression and impact of therapy on long-term outcome

Divergent data have been reported for fibrosis progression under IFN treatment. Samuel et al randomized 52 patients to treatment of HCV recurrence with IFN alpha-2b plus ribavirin at standard doses (n = 28) or no treatment (n = 24) for 12 months.⁹² Treatment resulted in an SVR of 21% without significant histological improvement between the treatment and control groups. Another study reported marked histological improvement in 86% of patients with SVR achieved

after 6 months of combined therapy, followed by 6 months of ribavirin.¹⁴⁸ Little impact on fibrosis has been observed by others.¹⁴⁹

Antiviral long-term medication is discussed controversially. In the non-transplant setting a subanalysis of the EPIC3-study, including 631 patients with liver cirrhosis and previous failure of IFN therapy, treated with 50 µg PEG-IFN, revealed no benefit for IFN long-term medication in prevention of hepatic decompensation.

Only patients who achieve SVR by antiviral therapy show significantly improved long-term outcomes with better 5-year survival rates.^{87,88,150}

Since steatosis and the metabolic syndrome are associated with fibrosis progression and post-LT diabetes mellitus (PTDM), metabolic syndrome should be treated.^{151,152} Avoiding steroids may improve the metabolic syndrome, the rate of fibrosis progression, and the incidence of PTDM. Hyperglycemia, hypertension, and body mass index can be reduced by physical exercise and diet.

Retransplantation

Indications for retransplantation due to disease recurrence remain unclear and differ among institutions. The prognosis for these patients is poor in comparison with the first transplantation.^{153–160} Many patients are not considered eligible for retransplantation and die from recurrent disease and its complications, but there are no recommendations or guidelines about retransplantation in these patients. The option of retransplantation is discussed on an individual base.

Factors affecting therapy

Duration of IFN therapy

There is no general recommendation for the duration and dosage of interferon therapy. Berenguer et al found that the strongest predictive factor of nonresponse is the lack of an EVR 3 months after start of therapy.¹³¹ For chronic hepatitis C in the nontransplant setting guidelines recommend that for patients who do not respond to therapy by week 12 (EVR with negative HCV-RNA or at least a 2 log₁₀ decrease from HCV-RNA at baseline), treatment should be discontinued because studies show that the negative predictive value of EVR is 97% to 100%.¹¹² Whether this 12-week stopping rule applies equally to transplant recipients with recurrent hepatitis C has not been conclusively determined, but data from recent studies suggest that the role of EVR in predicting treatment outcome among liver transplant recipients is comparable to

that in the nontransplant setting.^{104,106,107,110} EVR represents an important predictor of treatment outcome and may be considered a reliable indicator that treatment should be stopped if it is not attained. At present, attainment of EVR is the only factor shown by multivariate analysis to be significantly associated with SVR.¹⁰¹

Very few studies deal with the value of RVR in predicting treatment outcomes after LT. Hanouneh et al reported that RVR (defined as undetectable HCV RNA at week 4 of treatment) was a highly reliable predictor of treatment outcomes: all patients with undetectable HCV-RNA at week 4 attained SVR.¹⁶¹

Treatment with PEG-IFN plus ribavirin was administered in most studies over a duration of 12 months.^{94,96,98,99,101,104–110}

The question of whether genotype 2 and 3 can be treated for a shorter time or if it is necessary to prolong therapy in patients with delayed virological response and high baseline viral loads as recommended in the nontransplant setting remains also to be answered. In the transplant setting many studies pool genotype 1 and non-1, resulting in higher overall SVR rates, since genotype 2 and 3 are known to result in better SVR rates.¹⁶¹

Ribavirin dosing

After LT, ribavirin has to be carefully administered because transplant recipients are particularly susceptible to ribavirin-induced toxicity, predominantly hemolytic anemia, which is reported in 70% to 100% of treated patients.^{104,106,107,109} Thus it is difficult to balance the necessity for high-dose (>800 mg/day) ribavirin to attain high SVR rates against its extremely poor tolerability profile in these patients. Weight-based dosing is inadvisable because of the high treatment-related toxicity. Therefore many authors initiate ribavirin at low doses (400 to 600 mg/day) and slowly escalate according to toxicologic parameters (hemoglobin levels, renal insufficiency, creatinine clearance, and overall tolerability) over a period of several (usually 4) weeks.^{104,108–110}

Dose reductions, discontinuations and use of growth factors

Berenguer et al systematically analyzed studies evaluating antiviral therapies with PEG-IFN alpha in combination with ribavirin for the management of recurrent hepatitis C after LT.¹³¹ In 19 studies including 644 patients PEG-IFN alpha-2b was used in 16 studies: dose reductions were necessary in 73% of patients, and discontinuations occurred at 27.6% (mean SVR rate 30.2%).

The main causes of treatment discontinuation include cytopenia (particularly anemia), neuropsychiatric conditions, thyroid abnormalities, poor tolerability, and rejection episodes.¹³¹

Most transplant centers use growth factors to minimize the need for dose reductions or discontinuations. In 13 studies, where erythropoietin (EPO) was used, the overall SVR rate was 33% and was not statistically different from the rate of 29% described in 5 studies where it was not used.¹³¹ The granulocyte colony-stimulating factor filgrastim was given in 11 studies with a SVR of 34% compared to 29% in 7 in which it was not administered. Although the absolute SVR rates did not statistically differ, the authors concluded that there was a trend to better results, both in terms of SVR and rate of discontinuation, over time: the rate of SVR was 19.7% in studies published in 2004 and 2005 compared to 35.2% studies published in 2006 and 2007.

These results may reflect a learning process in managing therapy of recurrent hepatitis C after LT with a greater use of growth factors.

EPO and growth factors may be useful to ensure that patients receive adequate antiviral therapy over time and minimize the number of dose reductions and discontinuations.

Furthermore, thrombopoietin receptor agonists, such as eltrombopag, may be useful for improving pretreatment platelet counts in patients with hepatitis C and cirrhosis who would otherwise be ineligible for therapy.¹⁶²

Safety and tolerability

There is evidence that IFN therapy may enhance the likelihood of early acute graft rejection, with reported acute rejection rates up to 35% and chronic rejection rates up to 4%.⁴⁶ However, controlled trials show no differences in rejection rates between untreated and treated recipients.^{127,128} Furthermore IFN has been reported to induce immune-mediated cryptogenic hepatitis.^{163,164}

The tolerability of IFN treatment in combination with ribavirin is low and therefore dose reductions and discontinuation of treatment mainly due to hematologic toxicity and cytopenia are frequent.¹³¹ For patient-focused perspectives such as quality of life (QoL) or patient satisfaction, there are no published data for HCV-positive patients after LT, possibly due to the fact that these patients form a very heterogeneous group with numerous pathologies. Among the HCV-positive nontransplant population the effects of IFN-induced depression and anemia

on QoL are strong.¹⁶⁵ Despite a reduced QoL under IFN therapy, many transplant patients are highly motivated after LT.

Future perspectives

Specifically targeted antiviral therapy for HCV (STAT-C)

A broad set of new antiviral therapies is on the horizon, whereas new drugs, directly targeting HCV replication, have already demonstrated promising results. Directly acting antiviral agents are collectively described as Specifically Targeted Antiviral Therapy for HCV (STAT-C). Orally available small molecules, which specifically inhibit the HCV genotype 1 nonstructural (NS) 3/4A serine protease and NS5B RNA-dependent RNA polymerase, have advanced to phase 2 and 3 clinical development respectively.

The HCV-specific proteinase inhibitors telaprevir (VX-950) and boceprevir (SCH503034) are the most advanced drugs and have been investigated in the nontransplant setting in combination with PEG-IFN and ribavirin.

Telaprevir forms a covalently but reversibly bound complex with HCV protease. A 4.4 log₁₀ median reduction in viral load at day 14 of treatment has been shown in patients given 750 mg telaprevir every 8 hours, and an additional logarithmic reduction has been shown for telaprevir in combination with PEG-IFN.¹⁶⁶ The PROVE 1 (USA) and 2 (Europe) studies (telaprevir) included therapy-naïve patients with genotype 1 (n = 250/332), who were randomized in 4 treatment arms: PEG-IFN alpha-2a + ribavirin 1000 to 1200 mg for 48 weeks; telaprevir 750 mg (q8 h) + PEG-IFN + ribavirin for 12 weeks, followed by PEG-IFN + ribavirin for 12 weeks; telaprevir 750 mg (q8 h) + PEG-IFN + ribavirin for 12 weeks; telaprevir 750 mg (q8 h) + PEG-IFN for 12 weeks.^{167,168} Patients treated with telaprevir plus PEG-IFN and ribavirin for 12 weeks followed by PEG-IFN + ribavirin for 12 weeks showed higher SVR rates (61%/62%) compared to standard therapy, but the treatment was accompanied by a higher rate of side effects (PROVE 1: 13% vs 3%); especially rash or pruritus, gastrointestinal events, and anemia occurred more frequently.^{167,168}

Boceprevir is the focus of a large study (SPRINT-1; n = 595 treatment-naïve patients with genotype 1) with a complex design comparing standard therapy (PEG-IFN + ribavirin 800 to 1400 mg/day, 48 weeks) with 5 different treatment regimens of boceprevir (800 mg/day): 4 weeks PEG-IFN + ribavirin lead-in followed by PEG-IFN + ribavirin (800 to 1400 mg/day) + boceprevir for 24 or 44 weeks; PEG-IFN + ribavirin (800 to 1400 mg/day) + boceprevir for 28 or 48 weeks; PEG-IFN + low dose ribavirin

(400 to 1000 mg/day) + boceprevir for 48 weeks. Best results were obtained in the group with lead-in-phase followed by 48 weeks of triple therapy. SVR rates reached 75% in this treatment group compared with 38% under standard therapy. Boceprevir regimens significantly increased SVR with very low relapse rates.

Other nucleoside inhibitors and nonnucleoside, allosteric inhibitors of polymerase activity, have shown evidence of antiviral activity and are currently in clinical phase 1 and 2 studies (eg, ITMN-191, GSK625433, GS9190, R7128, TMC435350, R1626, VCH-759).

Host factor-targeting drugs

Besides STAT-C, host factor-targeting drugs and immunomodulatory approaches have been developed.

Cyclophilin inhibitors

The antiviral activity of nonimmunosuppressive cyclosporin analogs (NIM811; DEBIO-025) is also being investigated. These molecules disturb interaction of the replicase with cyclophilin B, a functional regulator of the HCV RNA-dependent RNA polymerase that is independent of the calcineurin–nuclear factor of activated T cells pathway involved in immunosuppression.¹⁶⁹

Glucosidase inhibitors

N-glycosylation of viral glycoproteins is important in viral morphogenesis, and inhibition of glucosidase 1 activity adversely affects viral maturation.¹⁷⁰ Celgosivir, a glucosidase 1 inhibitor, has shown synergy with interferon and ribavirin.¹⁷⁰

HCV-entry inhibitors

Events occurring during virus replication trigger the exposure of normally intracellular anionic phospholipids on the outer surface of virus-infected cells. A chimeric antibody, bavituximab (antiphosphatidylserine), identifies and targets the exposed anionic phospholipids.¹⁷¹

Activators of innate immunity/Toll-like receptor agonists

Immunomodulatory approaches that are being studied include agonists of Toll-like receptors (TLR), which activate pathways of innate, cellular, and humoral immunity. CpG oligonucleotides, which contain motifs resembling bacterial DNA, activate TLR-9 expressed in plasmacytoid dendritic cells and B cells.¹⁷²

New interferons

A novel recombinant protein that consists of interferon-fused to human albumin (albumin interferon) is in phase 3 trial. This agent has an exceptionally long plasma half-life,

which allows its administration every 2–4 weeks. In a study with 1131 treatment-naïve patients, the SVR rate with albumin interferon (dose 900 or 1200 µg every 2 weeks) was comparable with that of PEG-IFN α -2a treatment (48% and 51% vs 47%).

Other potential advances in interferon therapy include the development of novel interferons (gene-shuffled interferons) such as BLX-883 (locteron interferon) and a new administration route that involves implantation of a subcutaneous device that releases interferon over several months.¹⁷³

Ribavirin pro-drugs

Taribavirin is a prodrug that is converted to ribavirin and concentrated in the liver. In a phase III trial that compared treatment with either pegylated interferon PEG-IFN α 2b in combination with taribavirin versus ribavirin, taribavirin failed to meet noninferiority criteria for efficacy although superior hematologic safety was demonstrated.¹⁷⁴

A new era in the therapy of recurrent hepatitis C?

Although until now, to the best of our knowledge, there exist no clinical trials investigating STAT-C agents in patients who underwent LT for hepatitis C, these new drugs will offer efficient therapy to a wider patient group with better tolerability profiles and effectiveness in the near future. The introduction of targeted antiviral therapies for HCV and other new agents has the potential to lead to rapid viral clearance, increased SVR rates, and reduced duration of therapy. Earlier protease and polymerase inhibitors, and nucleic-based technology, have failed because of insufficient antiviral activity, or safety or delivery issues. Eventually some of the agents discussed here, or other promising approaches that are undergoing preclinical tests, will prove to be safe and effective. New rules for tailored HCV therapy will be established, facilitating highly individualized treatments that involve combinations of agents. It is certain that the new antiviral therapies will change treatment and viral kinetics before as well as after LT, especially for viral resistance. Moreover, side effects and treatment-induced anemia could affect therapeutic options of STAT-C in the transplant population.

So at this time it is too early to predict best therapeutic strategies of STAT-C or other drugs like cyclophilin inhibitors in this new era of HCV treatment in liver transplant patients with recurrent infection, possibly pretreated (or still under perioperative treatment?) with new agents. A combination of different treatment groups as well as perioperative treatment offer a number of possibilities, but the best therapeutic regimens need to be investigated and, so far, remain speculative. Overall the

current studies in the nontransplant setting indicate that PEG alpha and ribavirin remain the backbone of antiviral therapy of chronic hepatitis C even in the era of STAT-C. Promising combinations are protease inhibitors plus nucleoside analogue and nonnucleoside analogue polymerase inhibitors.

Conclusions

Recurrent hepatitis C after LT is a major cause of morbidity and mortality in the post-transplant setting. The clinical course after LT is highly variable and accelerated compared to the pretransplant setting. Although many risk factors have been identified, their accuracy in predicting the course in individual patients is uncertain. Diagnosis is based upon the detection of HCV-RNA and compatible histologic changes. Optimal treatment of recurrence is not defined. Published data suggest that the best available therapy is a combination of PEG-IFN plus ribavirin in patients with established recurrent hepatitis C (fibrosis stages ≥ 2) as proven by liver biopsy. Although increasing experience in using IFN therapy in the post-transplant setting has suggested better response rates, treatment is limited, especially after LT, by poor tolerability and high rates of severe side effects (mainly cytopenias), necessitating lower doses or withdrawal of therapy. The extent to which dose reductions affect SVR and the potential benefits of the concomitant administration of erythropoietin or granulocyte colony-stimulating factor in preventing complications or enhancing virological response is still to be determined. The optimal timing for the initiation of post-LT antiviral therapy still needs to be defined. Prophylactic or preemptive therapy is limited by the low applicability and tolerability and low rates of virological response, and is therefore not recommended.

Clinical trials comparing the safety and efficacy of antiviral therapy initiated prophylactically vs treatment of recurrent hepatitis C are lacking.

The therapy should be carried out only in transplant centers with experience in managing hepatitis C after LT.

There are promising data suggesting that in future, new classes of antiviral drugs such as HCV protease inhibitors will improve HCV therapy after LT.

Disclosures

The authors declare no conflicts of interest.

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