Review

Management of Chronic Hepatitis C in Cirrhosis and Liver Transplant Population

Shahid Habib, MD;[1] Obaid Shakil Shaikh, MD[2]*

[1] Divisions of Gastroenterology & Hepatology and Transplantation, University of Arizona, Tucson, AZ
[2] Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh School of Medicine, Pittsburgh, PA

Hepatitis C treatment has evolved tremendously since the discovery of the virus 24 years ago. Patients with cirrhosis, metabolic syndrome, co-infection with HIV, end stage renal disease and liver allograft recipients are particularly difficult to treat. At the same time, such patients often suffer from significant morbidity and mortality. This review primarily focuses on treatment of HCV infection in patients with cirrhosis and liver allograft recipients. First generation HCV protease inhibitors, boceprevir and telaprevir, improved sustained virologic response rates in both treatment naive and treatment experienced patients. However, both drugs are associated with significant adverse events and drug-drug interactions, thus limiting their use in patients with advanced liver disease and allograft recipients. The advent of highly effective and better tolerated oral anti-virals have dramatically enhanced treatment efficacy with response rates exceeding 90%. It is expected that such agents will significantly alter the outlook for difficult to treat HCV infected populations.

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INTRODUCTION

Hepatitis C virus (HCV) has global impact with an estimated prevalence of 2.8% and > 185 million individuals infected worldwide.[1] Interferons provided the mainstay of treatment since their efficacy in chronic non-A, non-B hepatitis was first noted almost 3 decades ago.[2] Isolation of HCV and an understanding of its genome and replication provided the basis for rapid progression in anti-viral therapy.[3] The introduction of directly acting agents (DAA) transformed treatment outcomes and response rates have improved from an abysmal 20% to those approaching greater than 95%.

Nonetheless, HCV infection in select populations remains challenging. Patients with advanced liver disease, and liver allograft and other organ transplant recipients are poorly tolerant to treatment and have low response rates. In contrast to interferons that mainly act by augmenting immune responses to viral antigens, DAAs act by inhibiting key viral enzymes and co-factors. First generation HCV protease inhibitors, boceprevir and telaprevir, were approved by the Food and Drug Administration in 2011. In combination with pegylated interferon and ribavirin, those agents resulted in improved efficacy and shortened duration of treatment.[5,6]

Recent approval of a second generation HCV protease inhibitor, simeprevir, and an HCV polymerase inhibitor, sofosbuvir, in combination with pegylated interferon and ribavirin, has further advanced treatment efficacy.[7,8] It is likely that in the not too distant future, HCV treatment will evolve into highly effective all oral regimen of 12 weeks with anticipated cure rate of almost 100%. As a result, the morbidity and mortality from HCV infection and the need for liver transplantation is expected to decline significantly during the next decade.

HEPATITIS C TREATMENT IN PATIENTS WITH CIRRHOSIS

What is the Urgency?

Natural history of HCV infection has been well studied. Patients with cirrhosis are at very high risk of further progression to decompensation and death. About 4% to 5 % of such patients decompensate annually if remained untreated.[9,10] The most common form of decompensation is ascites, followed by variceal bleeding, encephalopathy, and jaundice. Progression is accelerated in patients with other co-morbid factors such as obesity, metabolic syndrome, alcoholism, co-infection with HIV or HBV, and immunosuppression. Risk of developing hepatocellular carcinoma (HCC) is also high, ranging from 7% to 10%. Without liver transplantation, decompensated cirrhosis leads to death in 50% to 72% of patients after 5 years.[9] Liver transplantation is an option in selected group of patients with hepatic decompensation. A good proportion of patients do not meet eligibility criteria. Even patients who get listed for transplantation may not get transplantation and die on the wait list. Wait list mortality is not accurately reflected in Scientific Registry for Transplant Recipients (SRTR)

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***Corresponding Author:** University of Pittsburgh Medical Center, Kaufmann Building, Suite 916, 3471 Fifth Avenue, Pittsburgh, PA 15213. Tel: 412-647-4932. Fax: 412-647-9268. (Email: obaid@pitt.edu)

database as patients are often removed from the list when they get sicker. In many countries where HCV prevalence is high, liver transplantation has limited or no availability. Furthermore, HCV recurrence post transplantation is universal.[11] Almost 10% of liver transplant recipients develop severe early recurrence of HCV that is associated with very high morbidity and mortality. Among the remaining patients, almost 20% develop cirrhosis at 5 years post- transplantation. Treatment in HCV positive transplant recipients is extremely challenging with poor virologic response rate.[12]

What is the Benefit?

The goal of HCV treatment is to achieve sustained virologic response (SVR) that is defined as negative or undetectable HCV RNA by PCR at 24 weeks following completion of treatment. More recent studies have helped develop the concept of SVR 4 and SVR 12, defined as undetectable HCV RNA at 4 weeks and 12 weeks following completion of treatment, respectively. The sustainability of response determined by these goals has been well established.[13]

Histological improvement and fibrosis regression:

Regression of hepatic fibrosis in patients achieving SVR is well documented. In a pooled data analysis of four randomized clinical trials, 3010 patients were included with a mean follow up period of 20 months.[14] A large proportion of patients showed no change in the fibrosis stage, 20% showed regression, and 15% revealed progression. These results were independent of treatment response. In a well-designed prospective study, fibrosis regression was assessed in 38 paired pre- and post-SVR biopsies (analyzed at 61 months post-SVR).[15] Fibrosis regression was seen in 61% of patients and collagen content decreased in 89%. Another study showed even higher rate of regression at 5 years of follow-up.[16] Forty-nine out of 150 patients with paired pre-treatment and long-term follow-up biopsies were included and blindly rescored. Forty of those patients (82%) had a decrease in fibrosis score, and 45 (92%) had a decrease in combined fibrosis and inflammation score. Ten patients (20%) had normal or nearly normal livers on long-term follow-up biopsies. All patients with pretreatment cirrhosis or advanced fibrosis had improved fibrosis scores. Several other reports showed similar findings.[17,18]

Prevention of liver complications and HCC:

Data is growing as regards to the long term benefit of achieving SVR. Patients with compensated cirrhosis who achieve SVR essentially eliminate their subsequent risk of hepatic decompensation. The risk of hepatocellular carcinoma and the need for future liver transplantation also declines.[18-20] Antiviral therapy and attainment of SVR is also associated with reduction in hepatic venous pressure gradient and in the risk for development of esophageal varices.[21,22] In a study evaluating the benefits of HCV treatment in cirrhotic patients compared to those not treated, 54 HCCs and 66 liver transplants were prevented.[23] In a large cohort of treated patients with follow up of 10 years, only 7 patients with SVR and 76 without SVR developed HCC, with 10-year cumulative incidence of 5.1% and 21.8%, respectively.[24] Cumulative rate of hepatic decompensation at 10 years post-treatment in patients with and without SVR was 2.1% and 29.9%, respectively.

Survival benefit:

In a retrospective analysis, treatment of patients with compensated cirrhosis resulted in 119 fewer deaths as compared to patients who were not treated.[23] Survival benefit was best evaluated in a large multicenter international study.[24] Among 530 patients treated, 192 (36%) achieved SVR and in those patients 10 year all-cause mortality rate was 9% compared to 29% in those without SVR. Treatment was thus associated with reduced risk of all- cause mortality (HR 0.26).

Cost benefit:

In an interesting study, timing of HCV therapy in patients with advanced liver disease was assessed based on a decision analysis model.[23] A Markov model was constructed to compare treatment strategies: (1) no treatment, (2) antiviral therapy in patients with compensated cirrhosis, (3) antiviral therapy in patients with decompensated cirrhosis, and (4) antiviral therapy in patients with progressive fibrosis due to recurrent HCV post-transplantation. Compared to the no-antiviral treatment strategy, treatment during compensated cirrhosis increased quality-adjusted life years (QALY) by 0.950 and saved $55,314 whereas treatment in decompensated cirrhosis increased QALY by 0.044 and saved $5,511. Treatment during post-transplant severe recurrence increased QALY by 0.061 and saved $3,223. The model was sensitive to the rate of graft failure in patients with and without SVR. Thus, treatment of patients with compensated cirrhosis appeared to be the most cost-effective strategy.

What are the factors affecting HCV treatment outcome?

Several factors have been associated with poor SVR rates; among them are cirrhosis, metabolic syndrome, prior treatment failure and IL28b polymorphism. Patients who have multiple poor prognostic factors are harder to treat. Treatment of patients with cirrhosis has always been challenging because of higher chances of adverse events and increased likelihood of developing hepatic decompensation.[25] Decompensation rate of 12% has been reported in patients undergoing treatment with interferon based therapies.[26] In addition, SVR rates are inferior in patients with cirrhosis as compared to patients without cirrhosis regardless of genotype. In genotype 1 patients, SVR rates have improved with triple therapy (pegylated interferon, ribavirin and a protease inhibitor) but still remained lower compared to non-cirrhotics.

Several factors are expected to affect treatment course and outcome when treated with pegylated interferon and ribavirin combination in the setting of cirrhosis. In a multicenter retrospective cohort of 568 Spanish patients, multiple variables were assessed including portal hypertension, esophageal varices, prior treatment response, body mass index, diabetes mellitus, and center size.[27] Seventy percent of the population had genotype 1. Variables independently

associated with SVR in the entire cohort and in naive patients were non-genotype 1 (OR = 4.183), overall dose and time-of-treatment > 80% (OR = 3.177), serum GGT < 76 IU per ml (OR = 4.092), baseline viral load < 6×10^5 IU/mL (OR = 2.597), and the absence of ultrasound signs of portal hypertension (OR = 2.067).

What is the Effectiveness of Treatment Regimens?

Treatment efficacy in compensated cirrhosis with genotype 1:

Overall, dual therapy with pegylated interferon and ribavirin achieved SVR rates of 41% in genotype 1 and 73% in genotype 2 and 3 patients.[25,28] SVR rates were noted lower in patients with cirrhosis compared to those with mild to moderate fibrosis.[27] In genotype 1 patients, SVR improved with triple therapy that included one of the two protease inhibitors, telaprevir or boceprevir. However, all cirrhotic patients required treatment for 48 weeks.

In the SPRINT-1 phase II study, 7% of enrolled patients had cirrhosis, SVR rate was 67% in the combined 48-week boceprevir groups compared to 25% in the control group.[29] In the SPRINT-2 study, 8.8% of the cohort of 83 patients was identified to have stage-IV Metavir fibrosis score; SVR rates were 31%, 46% and 42% in the control group, response guided group and 48 weeks of triple therapy group, respectively.[5] Patients without cirrhosis had higher probability of achieving SVR (OR 2.5). In the RESPOND-2 phase III trial of 403 patients who were prior partial responders or relapsers to pegylated interferon and ribavirin, 12% had cirrhosis.[30] In the triple therapy group that included boceprevir, SVR was achieved in 77% of patients without cirrhosis compared to 66% in those with cirrhosis. Patients without cirrhosis had higher likelihood (OR 1.5) of achieving SVR compared to patients with cirrhosis.

In a phase III study (ADVANCE), 1088 treatment naïve HCV genotype 1 patients were randomized to be treated with pegylated interferon and ribavirin with or without telaprevir.[6] Among patients with bridging fibrosis or cirrhosis (21%), 62% treated with 12 weeks achieved an SVR. In a non-inferiority trial of telaprevir in 540 treatment naïve patients (ILLUMINATE), 149 (28%) had bridging fibrosis or cirrhosis; 94/149 (63%) had an SVR.[31] In PROVE 3 phase 2 study, 465 patients with non-response, relapse or breakthrough to prior therapy, were enrolled and 16% had cirrhosis.[32] In the 12 week telaprevir arm 53% of patients with cirrhosis had SVR compared to 45% in the 24 week arm. In the REALIZE phase 3 trial, 663 patients with prior non-response or relapse were enrolled and among them 25% had cirrhosis.[33] Patients with previous relapse showed higher SVR rate compared to non-responders (84% vs. 44%) whereas those with prior null response had SVR rate of 28%. The effect of hepatic fibrosis was most dramatic in the null responder group; among them 41% of those with mild fibrosis, 39% of those with bridging fibrosis and 14% of patients with cirrhosis achieved an SVR.

Efficacy of treatment in compensated cirrhosis and genotype non-1:

Efficacy of HCV treatment in non-1 genotype patients with cirrhosis is also inferior as compared to patients without cirrhosis.[34] In a systematic review, the overall SVR rate in patients with cirrhosis was 37% and it was significantly lower in patients with genotype 1 or 4 compared to those with genotype 2 or 3 (20.5% *vs.* 56.5%).[28] In a large retrospective study, among patients with cirrhosis those with genotype 1 showed inferior SVR compared to patients with non-1 genotype (25 % vs 55%). In genotype 5 patients, SVR is achieved in > 60% and in genotype 6 in 60-85%.[35] In a data review of three studies, lower SVR rates were seen in patients with cirrhosis and genotype 1/4 compared to those with bridging fibrosis and no significant fibrosis (33 %, 51% and 60%).[25] In genotype 2/3 patients, similar trend was observed (57%, 61% and 76%). In a meta-analysis, response to treatment in patients with genotype 5 was similar to genotype 1 patients but was inferior to patients with genotypes 2 or 3.[36]

Treatment of patients with decompensated cirrhosis:

There is no particular published data evaluating HCV treatment in this group of patients. In general, HCV treatment in patients with hepatic decompensation is contraindicated. However, some researchers have attempted to treat such patients, in particular those who had prior decompensation but compensated disease at the time of treatment initiation. Rationale to treat such patients is to achieve SVR or HCV PCR negative status prior to transplantation. In a series of 13 decompensated patients, all patients underwent splenectomy prior to initiation of treatment to improve thrombocytopenia.[37] Ten (76.9%) patients developed postoperative complications including minor portal vein thrombosis (2/13, 15.4%) and transient ascites (8/13, 61.5%). Eight (61.5%) patients achieved SVR, including all HCV genotype 2a-infected patients (4/4, 100%) and some of the genotype 1b-infected patients (4/9, 44.4%). Treatment was temporary held because of severe intestinal infection. In a meta-analysis, the proportion of patients who needed to discontinue their therapy due to SAEs was significantly higher in patients with Child-Pugh class B and C vs those with Child-Pugh class A- 22% vs 11.4%. Overall, SVR rate was 37% in the entire cohort of cirrhotic patients.[26]

What are the Challenges?

Hepatic decompensation and mortality is the biggest concern when treating patients with cirrhosis, requiring close monitoring and expertise to manage adverse events and complications. It is preferred that such patients be treated in a specialized unit where back up support for liver transplantation is available if needed.

Hepatic complications and adverse events with dual therapy:

In a large Spanish cohort, hepatic decompensation rate was 12% manifested by ascites and encephalopathy. Variceal hemorrhage developed in 4%, almost 6% were diagnosed with HCC during the course of treatment and about 6% died because of liver related complications.[27] Adverse event rate was 18% and overall drop-out rate was 30% which was less as compared to other reports.[25,38] Surprisingly only one

patient decompensated, no one developed variceal hemorrhage and acute flares of aminotransferases were rare.

In a recent systematic review, treatment course of 1133 HCV genotype 1-4 cirrhosis patients from 17 clinical trials were reviewed.[28] All patients had received treatment with combination of pegylated interferon and ribavirin. Treatment discontinuation rate was 14.5% and hepatic decompensation rate was 12%. The most common serious adverse events were: thrombocytopenia and/or neutropenia (23.2%), psychiatric disorders (15.5%), and severe anemia (11.2%). Patients with Child's class B and C had higher tendency to discontinuation compared to Child's class A patients (22% vs. 11.4 %). In a randomized controlled trial, IL28b and inosine triphosphate (ITPA) genetic polymorphism and portal hypertension were associated with severe anemia and higher rates of adverse events.[39] ITPA genetic variants have high enzyme activity leading to severe anemia requiring dose reduction and eventually treatment failure.

Low platelet count is one of the limiting factors for the use of interferon based antiviral therapy. Researchers evaluated the efficacy of eltrombopag in patients with cirrhosis to help initiate and maintain HCV treatment. The drug reduced the need for platelet transfusions in thrombocytopenic patients with advanced liver disease undergoing invasive procedures. It also helped increase SVR to interferon-based antiviral therapy in patients who were poor candidates to treatment because of thrombocytopenia.[40,41] The role of splenectomy has also been evaluated and it indicated that splenectomy prior to interferon-based therapy was safe and may facilitate adherence to subsequent antiviral therapy in selected HCV cirrhotic patients with portal hypertension and hypersplenism.[37]

Treatment of Cirrhosis: Future Directions

Many second- and third-generation DAAs with less complex dosing, tolerable side effect profile, and fewer drug–drug interactions are in various phases of development, currently. Sofosbuvir, an HCV polymerase inhibitor, and simeprevir, a protease inhibitor, were recently approved by the FDA in United States. There is limited data for their efficacy in patients with cirrhosis.

Sofosbuvir is a potent nucleotide analogue that inhibits HCV NS5b polymerase. It is approved for use in combination with pegylated interferon and ribavirin in all genotypes. Efficacy of this combination is higher even with shorter duration of treatment and with less adverse events. In phase II trial in non-cirrhotic patients, SVR rate was 90% and without any difference between 12 weeks and 24 weeks duration of therapy.[42] In another phase II study, sofosbuvir 400 mg/day in combination with pegylated interferon and ribavirin for 12 weeks in genotype 2 and 3, and response guided treatment in genotype 1 patients for 24 to 48 weeks produced SVR rate of >90%.[43] In a non-inferiority trial, patients with genotype 2 or 3 infection who received either sofosbuvir or pegylated interferon and ribavirin, had nearly identical rates of response (67%).[7] Phase III studies of sofosbuvir in genotype 2 and 3 patients for a period of 12 weeks to 16 weeks have revealed response rates of around 70% with lower response rates observed in genotype 3 patients. Additionally, in genotype 3 patients response rates were lower among patients with cirrhosis. In another study, patients with advanced fibrosis had higher rate of relapse.[44]

HCV TREATMENT IN LIVER TRANSPLANT RECIPIENTS

What is the Urgency?

Chronic hepatitis C has been the leading indication for liver transplantation. Histologic recurrence of HCV infection is universal and it usually develops within few months following transplant. Unfortunately, the course of HCV infection in liver allograft is often aggressive resulting in lower rates of graft and patient survival compared to patients without HCV infection. Outcome of HCV infection in liver allograft recipients is well studied and beyond the scope of this paper. Patients with severe recurrence and those with evidence of rapidly progressive fibrosis require emergent therapy. Severe cholestatic hepatitis develops in about 10% of HCV infected graft recipients usually within six months of transplantation. It results in graft loss if left untreated.[45] The median time to recurrent cirrhosis is 8–10 years, but 'rapid progressors' develop recurrent cirrhosis within 3-5 years.[12,46] Once patients reach the stage of allograft cirrhosis, 30-42% decompensate within the following year with 60% dying within the first year of decompensation.[12,47,48]

What is the Benefit?

Patients who achieve SVR either pre- or post-transplantation, have graft and patient survival similar to those without HCV infection.[49] In a retrospective study, patients receiving antiviral therapy for more than 48 weeks had remarkably improved survival regardless of SVR and patients with SVR had the best survival.[50] Histologic regression in patients who have achieved SVR has been reported in few studies. In a study of treatment with interferon and ribavirin, 100% of patients with SVR achieved a histological response (fibrosis stabilization or improvement) with a significant reduction in mean staging value (from 2.1 to 1.0). Histological response was observed in 84% of long-term treated patients compared to 57% of patients who dropped out. In another study, achieving SVR status was associated with reduced risk of fibrosis (worsening by 2 points or progression to stage 4/6 or higher) when compared to viremic patients.[51]

What is the Efficacy of HCV Treatment in Allograft Recipients?

In past two decades, multiple approaches to treat recurrent HCV infection in liver allograft recipients have been studied. This includes early preemptive treatment approach and delayed treatment approach. Preemptive approach entails treating patient within six months of transplantation prior to emergence recurrence of infection.[52,53] Delayed treatment refers to initiating treatment when there is significant histologic evidence of recurrent infection. Preemptive approach does not appear to offer any advantage.[54] Several treatment regimens have been studied including interferon monotherapy, ribavirin monotherapy, standard interferon with ribavirin, pegylated interferon monotherapy, pegylated

interferon in combination with ribavirin, and ribavirin maintenance therapy after 12 months of combination therapy. Overall none of those approaches have shown remarkably improved SVR. A pooled analysis of nearly 50 treatment trials estimated that SVR rates with ribavirin given in combination with standard interferon or pegylated interferon were 24% and 27%, respectively,[55] A meta-analysis (2004-2007) showed cumulative SVR of 30.2% (range: 0% to 50%).[56] Another meta-analysis revealed a cumulative SVR of 41% overall; genotype 1 patients had SVR of 29%, whereas in genotype 2 and 3 patients SVR was 100%.[57] Several factors have been associated with SVR including non-1 genotype, donor age < 60 years, donor IL28b genotype CC and rapid virological response (RVR) at 4 weeks.[58] Other factors include recipient IL28b genotype CC, low pretreatment viral load, mild histologic disease, cyclosporine immunosuppression and absence of drug interruptions or dose reductions. Thus, treatment of recurrent chronic hepatitis remains challenging with poor SVR rates especially in patients with multiple poor prognostic factors.

A multicenter trial evaluated the safety and efficacy of boceprevir or telaprevir in a small cohort of patients with genotype 1 recurrent hepatitis C.[59] Among 37 patients enrolled, 16 discontinued treatment due to treatment failure or intolerance. Seventy one percent and 20% achieved SVR 12 in patients who received boceprevir or telaprevir, respectively. Results of multicenter CRUSH-C study were presented at EASL.[60] This study included 112 patients with HCV genotype 1 (55% with harder-to-treat subtype 1a) and majority had multiple poor prognostic factors. At week 4, 66% had undetectable HCV RNA and at week 12, 84%. Extended rapid virologic response (eEVR) was achieved in 64%. Interim analysis showed overall SVR4 of 65%, and it rose to 93% among those with eEVR status. SVR4 was low at 44% in patients with cirrhosis or severe cholestatic hepatitis.

What are the Challenges?

Treatment of recurrent hepatitis C in liver allograft recipients remains challenging in view of poor tolerance to interferon based regimen and suboptimal efficacy. Most of the published studies are observational and retrospective analyses. Severity and spectrum of adverse reactions are exaggerated in the immunosuppressed liver recipients. Severe anemia requiring blood transfusion, acute rejection events, infections and higher rates of premature treatment discontinuation are common to treatment with combination of interferons and ribavirin. The addition of HCV protease inhibitors, telaprevir and boceprevir, increased the complexities. Three major issues encountered are severe anemia, drug-drug interaction between calcineurin inhibitors and protease inhibitors, and serious infections.[59] In healthy volunteers, co-administration of boceprevir increased cyclosporine bioavailability by 3 fold and bioavailability of tacrolimus by 17 fold.[61] Telaprevir increased the bioavailability of cyclosporine by 4.6 fold and of tacrolimus by 70 fold.[62] Thus, triple therapy in immunosuppressed patients require very close monitoring of drug level and dose titration of calcineurin inhibitors. In a multicenter trial, triple therapy was associated with serious adverse events in 21% necessitating hospitalization, 4% experienced liver graft rejection, and 6% died during follow-up.[60] Another multicentre study evaluating 112 patients reported similar spectrum of adverse reactions and safety profile. Liver related mortality was noted in 5.7%, treatment discontinuation in 20%, treatment interruption in 30%, erythropoietin use in 82%, blood transfusions in 52%, and graft rejection requiring treatment in 3.3%.[63]

What is the Future Direction of HCV Treatment in Liver Allograft Recipients?

Therapeutic options for HCV are expanding rapidly. Already, two new DAAs sofosbuvir and simeprevir are available for use in combination with pegylated interferon and ribavirin. Several new agents are under development. It is expected that interferon free, all oral regimens of 12 weeks to 24 weeks duration will soon be the standard of care. Those regimens will have higher efficacy and improved tolerability. We are at the cusp of development of such regimens that will be particularly suited for difficult to treat populations such as transplant recipients. In an early report of a multicenter study, 45 liver transplant recipients received sofosbuvir and ribavirin with or without pegylated interferon.[64] Seventy eight percent were noted to be HCV RNA negative at less than 12 weeks of treatment. Forty-seven serious adverse events were reported and 7 patients died likely due to progressive disease.

CONCLUSIONS

Hepatitis C patients with cirrhosis are at risk of death if left untreated. A large proportion of such patients have prior failure to treatment with pegylated interferon and ribavirin. The efficacy of retreatment with first generation protease inhibitors in combination with pegylated interferon and ribavirin also remained suboptimal. Viral clearance in such patients provides survival benefit and improved quality of life and it may obviate the need for transplantation. Treatment of recurrent hepatitis C in liver transplant recipients is particularly challenging in view of poor tolerability and drug interactions with the calcineurin inhibitors. However, the future of HCV therapy is promising in view of the development of highly effective and better tolerated oral agents.

CONFLICT OF INTEREST

None.

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