Management of Hepatitis C in the Pre- and Post-Transplant Setting: Then and Now

Abstract
The prevalence and accelerated course of recurrent hepatitis C infection after liver transplantation is associated with significant morbidity and mortality. Use of dual therapy with interferon/ribavirin or triple therapy with first-generation NS3/4 protease inhibitors for the treatment of hepatitis C in cirrhotic and post-transplant patients has yielded only modest sustained virologic response (SVR) rates. The advent of multiple new direct-acting antiviral agents has led to improved treatment outcomes in patients with chronic hepatitis C, all while minimizing undesired side effects and adverse reactions. This review describes the treatment of hepatitis C in cirrhotic patients awaiting transplantation and in patients with recurrent HCV after transplantation and the role of new all-oral therapy in both of these patient populations.

Keywords
Recurrent hepatitis C; Liver transplantation; Interferon-free regimen; Direct-acting antiviral agents

Introduction
Recurrent hepatitis C virus (HCV) infection after liver transplantation is the most frequent cause of death and graft and represents two-thirds of graft failures [1]. The recurrence of hepatitis C virus in a patient after liver transplant is associated with significant morbidity. It is estimated that at one year after orthotopic liver transplantation (OLT), more than 50% of patients with a history of hepatitis C prior to transplant will show histological evidence of HCV recurrence [2]. Of particular significance is the accelerated course of HCV recurrence in this setting [3]. Recurrence of HCV infections in the graft has been seen as early as four weeks after liver transplantation. It is estimated that 10% to 40% of patients will progress to cirrhosis within 5-10 years of transplant [4,5]. Previous studies have shown that HCV genotype 1b-infected liver recipients are at a high risk of developing graft cirrhosis in the first 5 years after transplantation, especially those with previous rejection episodes [6]. Certain factors have been proposed to be associated with an accelerated progression of fibrosis in patients with recurrent HCV infection, resulting in graft loss [7]. High HCV RNA levels in both serum and the graft at the time of or early after transplantation are associated with an increased risk of progression to cirrhosis, graft loss and death [8]. Other factors associated with poorer outcomes include female gender, older donor age, steatosis of the graft, the degree of HLA matching, and the IFN A 3 of the donor and the recipient [5,9,10]. Furthermore, rates of decompensation in patients with graft cirrhosis are particularly high, at approximately 42% at 12 months, further adding to morbidity [11].

The impact of preservation injury on the severity of recurrent hepatitis C after OLT has also been evaluated. A review of patients undergoing OLT for hepatitis C infection showed that the duration of ischemic rewarming during graft implantation was significantly associated with the severity of recurrent hepatitis C [12]. In their study, cold ischemia time did not correlate with the severity of hepatitis C. In the post-transplant setting, use of intravenous steroids for management of acute allograft rejection has been associated with an earlier recurrence of hepatitis C [13]. The type of calcineurin inhibitor used in the post-OLT setting and its effects on progression of fibrosis has also been assessed. Several prospective studies have concluded that there is no difference in incidence of advanced fibrosis with use of cyclosporine versus tacrolimus-based immunosuppressive regimens [14-16]. A retrospective review of 141 patients undergoing OLT for hepatitis C cirrhosis looked at the effect of sirolimus-based immunosuppressive regimens on post-transplant HCV recurrence in these patients [17]. Of note, sirolimus did not significantly affect the timing or severity of HCV recurrence and, in fact, sirolimus-treated patients had lower progressive activity and fibrosis level on serial biopsy. The effect of OKT3 on hepatitis C recurrence has been well-documented. Cohort studies have shown earlier and more severe allograft hepatitis in patients receiving OKT3, with patients exhibiting greater histological severity scores [18].

Although obtaining an SVR in patients with HCV recurrence in the post-transplant setting can greatly improve overall survival, this has only been reported in approximately one-third of patients (20-30% in genotype 1 and 40-50% in genotype 3) [19]. Up until recently, dual therapy with interferon/ribavirin (IFN/RBV) or triple therapy with first-generation NS3/4 protease inhibitors...
(PIs) were considered the most potent options available to these patients. Recently, multiple, new direct-acting antiviral agents have entered the hepatitis C arena.

This review describes the treatment of HCV in cirrhotic patients awaiting transplantation and recurrent HCV after transplantation and the role of new all-oral therapy in both of these patient populations.

**Treating Hepatitis C in the Pre-Transplant Period**

The current approach to the management of chronic HCV-infected patients undergoing transplantation includes pre-transplant antiviral therapy given in an attempt to prevent reinfection. Simply decreasing the HCV viral load prior to transplantation may not be enough to alter the course of HCV recurrence in the post-transplant setting [20]. Viral undetectability and achieving an SVR prior to transplantation has been shown to eliminate the risk of HCV recurrence [21]. Thus, it has been the primary goal in this particular setting.

**The use of traditional agents in the pre-transplant period**

Until 2011, dual therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care. The limitations of this therapy were that treatment was restricted to patients with compensated cirrhosis, given serious complications associated with treatment of decompensated cirrhotic patients. Despite the improvement after dual therapy, the SVR was lower in patients with compensated cirrhosis (43%-50%) than in patients without cirrhosis (57%-65%), with genotype 1 patients faring rather poorly with an SVR of 11% [22].

Two well-known trials looking at dual therapy (IFN/RBV) for patients with HCV cirrhosis were by Everson and Forns. Everson treated 124 decompensated cirrhotic patients with a mean MELD of 11, with IFN/RBV as part of the LADR regimen (low-accelerating dose regimen) [23]. Similar to prior studies, patients with HCV genotype 1 had worse SVR rates (24% in genotype 1 versus 50% in patients with genotypes 2/3). Fifty-seven patients were HCV RNA negative at the end of treatment with 27 patients achieving an SVR. Thirty patients recurred for a relapse rate of 53%. In another study, Forns treated 30 patients for a median of 12 weeks of IFN/RBV. SVR only occurred in 30% of patients and two-thirds of that subset being free of HCV recurrence in the post-transplant period. This further solidifies the notion that viral undetectability is key. Dose reductions were required in 60% and 20% stopped their therapy prematurely [24].

In this population, adverse reactions reduced adherence to therapy and resulted in dose modifications that resulted in less response. Dose reductions were required in more than half of patients that were treated. This belabors the point of interferon-related adverse reactions. These typically include bone marrow depression, flu-like symptoms, neuropsychiatric disorders, and autoimmune syndromes among others. The major issues that patients on ribavirin encounter are hemolytic anemia and rash. Because of the side effects, 10-20% withdraws from therapy prematurely and upwards of 20-30% of patients have required dose modifications [25]. Treatment-related decompensation is also a serious concern and has made providers gun-shy in proceeding with treatment. Table 1 refers to some of the most common adverse reactions associated with use of PEG-IFN and ribavirin.

Two first-generation protease inhibitors (PI), boceprevir and telaprevir, were FDA-approved in 2011 for patients infected with HCV genotype 1 in treatment naïve, non-responders and relapers. But in December 2012, a black box warning was placed on telaprevir in that some rashes may lead to death [26]. Boceprevir and telaprevir were each paired up with IFN/RBV as part of a triple regimen and results have seemed promising in the registration trials, as SVRs increased by 30% with triple therapy compared to PEG-IFN/RBV in treatment-naive patients and by 25-60% in treatment-experienced genotype 1 patients [27-30]. However, such results came a significant cost, as new issues once again surfaced. A two-fold increase in anemia was seen as well as the emergence of new adverse reactions. Dysgeusia was observed in nearly one-third of patients on boceprevir and a cutaneous rash in 55% of patients on telaprevir [27,28]. In patients with advanced fibrosis and cirrhosis, the triple regimen was a step up from the dual regimen, as this was an additional option that increased SVR in comparison to IFN/RBV regimens in genotype 1 patients with compensated cirrhosis. However, limitations included: (1) patients required careful monitoring, (2) previous non-responders would likely not benefit and (3) triple therapy would not be recommended in patients with decompensated cirrhosis [31].

Crippin’s observations in a pilot study of antiviral therapy in HCV infected patients awaiting liver transplantation noted that more than half of the patients awaiting liver transplantation had one or more contraindications to treatment with interferon with or without ribavirin [32]. The study also observed a high incidence of adverse events in patients with decompensated cirrhosis.

| Adverse Reactions            | Incidence |
|------------------------------|-----------|
| Anemia                       | 20-30%    |
| Headaches                    | 47-62%    |
| FEVERS                       | 40-46%    |
| Myalgia                      | 37-56%    |
| Rigors                       | 24-48%    |
| Arthralgia                   | 24-34%    |
| Nausea                       | 35-43%    |
| Depression                   | 22-31%    |
| Weight Loss                  | 29%       |
| Insomnia                     | 33-40%    |
| Alopecia                     | 21-36%    |
| Rash/dermatitis              | 20-24%    |
| Injection site inflammation  | 25%       |
| Pruritus                     | 25-29%    |
| Dyspnea                      | 26%       |
| Fatigue                      | 48-64%    |

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during treatment with antiviral therapy, thus concluding that anti-viral therapy is poorly tolerated in this population.

Another study looking at the tolerability and safety of antivirals and the first generation protease inhibitors was the CUPIC (Compassionate Use of Protease Inhibitors in viral C cirrhosis) cohort study which looked at treatment-experienced cirrhotic patients with genotype 1 [33]. In the intent to treat analysis, in the 292 patients treated with telaprevir, RNA was undetectable in 55.1%, 80.5%, 78.8%, and 67.1% at weeks 4, 8, 12, and 16. In the 42 patients treated with a lead-in phase, 9.5%, 76.2%, 71.4% and 59.5% were undetectable. In the 250 patients treated without a lead-in phase, 62.8%, 81.6%, 80.0%, and 68.4% had a response rate. At week 16, the response rate was significantly higher in relapsers (74%) than in partial responders (66.2%) and in null responders (45%). In patients treated with boceprevir, 2.4%, 37.6%, 54.6% and 58% showed response at 4, 8, 12 and 16 weeks. At week 16, response rate was significantly higher in relapsers (69.0%) than in partial responders (50.0%) and in null responders (22.2%) [33].

The safety profile was noted to be poor, with severe infection and hepatic decompensation in approximately 6% of patients. The CUPIC study suggested that treatment-experienced patients with compensated cirrhosis with platelet counts < 100,000/mm³ and serum albumin < 35 g/L may not benefit from triple therapy regimens [33].

The current wave of treatment in the pre-transplant period

The current wave of NS3/4A protease inhibitors and NS5B polymerase inhibitors have seen several advantages over the first generation PI’s. They include a higher barrier to resistance, better effectiveness with pan-genotypic activity, more convenient dosing, reduced pill burden, and better safety and tolerability [34-36]. In a large phase 2b study of 462 total patients, 93 treatment-experienced genotype 1 patients with cirrhosis were treated with simprevir (TMC435) 100 or 150 mg QD with PEG-IFN/RBV for 12, 24 or 48 weeks, followed by PEG-IFN/RBV until week 48 if needed vs PEG-IFN/RBV for 48 weeks [37]. SVR24 was noted to be higher in the simprevir regimen than with PEG-1NF/RBV. The SVR rate in patients with cirrhosis was reported to be 70-73% in patients with relapse, 15-82% in partial responders and 31-46% in non-responders.

Phase 3 data from QUEST 1 and QUEST 2 illustrated that simprevir in combination with IFN/RBV, led to SVR12 rates of approximately 60% in HCV patients with METAVIR scores of F4 [38,39]. In phase 3 data from the PROMISE study of patients who had previously experienced a relapse after prior treatment with IFN based therapy achieved a SVR 12 in 74% of patients with a METAVIR score of F4 [40].

In the NEUTRINO trial, NS5B pyrimidine nucleotide analogue, sofosbuvir 400 mg daily plus IFN/RBV was used for 12 weeks in 327 treatment-naïve patients with genotypes 1, 4, 5 or 6. Of these patients 17% had cirrhosis with a robust 81% response rate noted in the genotype 1 patients with cirrhosis. In the FISSION trial, sofosbuvir 400 mg daily plus RBV was used for 12 weeks in genotype 2 and 3 patients [41]. Twenty percent of the 256 patients that underwent this treatment had cirrhosis. The response rate was noted to be lower in genotype 3 then in those with genotype 2 (56% vs 97% respectively) and were lower for patients with cirrhosis than for those without cirrhosis (47% vs 72%). This highlights the continued difficulty in treating this population of patients.

As illustrated above, sofosbuvir has proven to have potent antiviral activity across all HCV genotypes. An open-label phase 2 study (2025) enrolled 61 compensated cirrhotic patients who were listed for transplantation due to hepatocellular carcinoma (HCC). Seventy-three percent of the patients were genotype 1 [37]. Patients received sofosbuvir 400 mg daily plus weight-based ribavirin 1,000-1,200 mg daily for a duration of 48 weeks, with the last dose given on day of transplant and the standard immunosuppressive medication used post-transplant [42].

Ninety-three percent of patients had an undetectable viral load at the time of transplantation, irrespective of the duration of the treatment. In those patients with an undetectable viral load at time of transplant, two-thirds of patients maintained viral suppression at 12-weeks post-transplant. A multivariate analysis showed that duration of viral undetectability was the only factor to significantly predict SVR and no HCV recurrence [42].

The LONESTAR study looked at 40 patients of which about half with cirrhosis who were not able to achieve a cure with the standard of care at that time, triple therapy (PI + PEG IFN/RBV). These patients were treated with sofosbuvir 400 mg and ledipsavir 90 mg daily with or without RBV for 12 weeks. The SVR12 was 91% in the cirrhotic patients. This proves that for a large portion of patients that RBV can be removed without affecting the SVR [43].

In the meantime, recent AASLD guidelines state that treatment-naive patients with compensated cirrhosis, including those with HCC, should receive the same treatment as recommended for patients without cirrhosis. This regimen consists of daily sofosbuvir, 400mg plus weight-based RBV for up to 48 weeks [44]. This was supported by Curry in his reporting that 93% of patients having undetectable RNA at the time of transplantation with two-thirds maintaining viral suppressions at 12 weeks post-transplantation [42]. Figure 1 summarizes the effect of various treatment regimens on SVR rates in patients with hepatitis C and advanced fibrosis.

Traditional Approaches to HCV Management in the Post-Transplant Setting

Obtaining a sustained virological response has been the primary goal in liver transplant recipients with recurrent hepatitis C, as this can greatly improve graft survival [19]. Unfortunately, achieving an SVR in this subset of patients is especially difficult. In the past, there have been two general approaches to treatment in the post-transplant setting: (1) a prophylactic treatment approach and (2) initiation of treatment after documentation of HCV recurrence and associated graft fibrosis. The PHOENIX...
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A cohort of 37 OLT patients with recurrent HCV, genotype 1b patients, were treated with triple therapy with either telaprevir or boceprevir, with end of treatment responses of 40% and 72% respectively [51]. The most common adverse event in the study was anemia (92%), highlighting again one of the limitations of a ribavirin-based regimen. The inherent risk of infection in the immunocompromised OLT patient as well as drug-drug interactions made implementation of such triple regimens especially difficult. Premature discontinuation of triple therapy for HCV recurrence in the post-OLT setting has been as high as 20%, despite fairly decent SVR12 rates [52]. The CRUSH-C multicenter study was undertaken to evaluate protease inhibitor-based triple therapy in a cohort of liver transplant recipients. Adverse events were common in this cohort, with 11% discontinuing treatment and 21% of patients experiencing serious adverse events requiring hospitalization [53]. More recently, the REFRESH study, a phase 2B, prospective, multicenter study, assessed the efficacy of telaprevir in combination with PEG-interferon and ribavirin in liver transplant patients with genotype 1 chronic HCV infection who did not have cirrhosis [54]. An interim analysis at week 16 was presented at AASLD in 2013. Conclusions included that the CYP3A4 inhibitory activity of telaprevir required substantial dose adjustments for each of the calcineurin inhibitors being studied. Tacrolimus required greater modifications of dose and dosing intervals than did ciclosporine. This is further evidence that the use of protease inhibitors in the post-transplant setting requires constant dose adjustments. This is also relevant in the setting of combined liver-kidney transplant recipients with recurrent hepatitis C [47], where treatment for hepatitis C has generally been avoided due to interactions between available antiviral agents and immunosuppressive medications.

New Approaches to Treatment in the Post-Transplant Setting

The last two years has seen the development of multiple new direct-acting antiviral agents for the treatment of hepatitis C. Table 2 refers to some of the newer agents being evaluated for the treatment of hepatitis C. Charlton et al. [8,54] recently reported an open-label phase 2 study of 40 OLT patients, with more than 90% exhibiting HCV genotype 1 and the overwhelming majority being treatment-experienced [55]. Their patients were treated with once daily sofosbuvir (400mg daily) plus ribavirin (started at 400mg daily, gradually increased based on tolerability). Taking into account its potentially limited clinical utility, SVR4 rates were noted to be 77% in their patient population. Of note, no interactions were reported between sofosbuvir and any immunosuppressant agents.

Strategies for implementation of these new direct-acting antiviral agents have also included IFN-free, ribavirin-free, combination therapy. The NS5B nucleotide inhibitor, sofosbuvir, has been shown in multiple studies to lead to high SVR rates without the need for interferon-based regimens [41,56]. Daclatasvir, a potent oral NS5A inhibitor, has been paired up with sofosbuvir for the treatment of recurrent HCV. SuKowskii et al. [56] conducted an open-label study of more than 200 patients assigned to sofosbuvir and daclatasvir, with or without ribavirin, for duration of 24 weeks [57]. SVR rates were consistently 90% or greater across genotypes 1, 2, and 3, including patients with no response to prior therapy with telaprevir or boceprevir.

Such a regimen has crossed over to the post-OLT setting.
as well. Fontana et al [57] reported the first ever use of an interferon-free, all oral 24-week regimen of daily sofosbuvir and dasabuvir in an OLT patient with recurrent cholestatic hepatitis C [58]. Viral load was undetectable within 4 weeks of treatment and the patient achieved sustained viral response, all the while his immunosuppression (tacrolimus) remaining unscathed. Studies focusing on the pharmacokinetics of newer DAAs such as dasabuvir have emphasized the lack of clinically-evident drug-drug interactions associated with its use alongside calcineurin inhibitors [59]. Understandably, SVR4 rates are not the best predictors of treatment success but the trial has pointed to an all-oral, IFN-free regimen as a treatment option for HCV recurrence in the post-transplant setting.

Entering the arena as of late has been the emergence of ABT combination therapy for the management of recurrent hepatitis C. In an ongoing phase II study, Kwo et al [60] are evaluating 34 post-liver transplant patients with recurrent genotype 1 HCV infection, who are receiving ABT-450 (an NS3/4A protease inhibitor), ritonavir, ombitasvir (an NS5A inhibitor), with dasabuvir (an NS5B RNA polymerase inhibitor) and ribavirin for a duration of 24 weeks. RVR was 100% and SVR12 has been reported to be 96% in this ongoing study.

In early 2014, the American Association for the Study of Liver Diseases (AASLD), in collaboration with the Infectious Diseases Society of America (IDSA), presented their recommendations for patients who develop recurrent HCV infection post-liver transplantation. For treatment-naïve patients with HCV genotype 1 in a compensated allograft liver, daily sofosbuvir (400mg)+plus simprevir (150mg), with or without ribavirin (initial dose 600mg, increased monthly as tolerated to weight-based dose), for 12 to 24 weeks was recommended [Class IIB, Level C recommendation] [44]. One of the bolder statements in the recent AASLD recommendations is that telaprevir or boceprevir-based regimens should not be used for patients with compensated allograft hepatitis C infection. This further supports concerns regarding adverse effects and drug-drug interactions associated with first generation protease inhibitors in this patient population.

We closely follow the AASLD’s recommendations when treating our own post-transplant patients with evidence of recurrent hepatitis C infection. Genotype 1 patients are typically started on daily sofosbuvir and simprevir for a duration of 12 to 24 weeks. Daily sofosbuvir and ribavirin for a duration of 12 and 24 weeks is used for our genotype 2 and 3 patients, respectively. In parallel with the AASLD recommendations, we do not use of telaprevir or boceprevir in this patient population.

Conclusion

Patients in the pre- and post-OLT setting with HCV recurrence may stand to benefit from implementation of new, recently-approved direct-acting antiviral agents. This is especially important given that the management of OLT patients, from the standpoint of immunosuppression management, is becoming more and more sophisticated with new agents continuously being developed. Appropriate treatment of recurrent hepatitis C in the pre- and post-transplant setting will certainly help minimize graft failure and prevent morbidity and mortality, especially if these new agents can peacefully co-exist with immunosuppression. Unequivocally, we are in the dawn of a new era for this special population of patients.

References

1. Grebely J, Dore GJ (2011) What is killing people with hepatitis C virus infection? Sem in Liver Dis 31(4):331-339.
2. Gane EJ, Portmann BC, Naoumov NV, Smith HM, Underhill JA, et al. (1996) Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med 334(13):815-820.

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3. König V, Baudet J, Lobeck H, Lusebrink R, Neuhaus P, et al. (1992) Hepatitis C virus reinfection in allografts after orthotopic liver transplantation. Hepatology 16(5): 1137-1143.

4. Berenguer M, Lopez-Labrador FX, Wright TL. (2001) Hepatitis C and liver transplantation. J Hepatol 35(5): 666-678.

5. Gastroenterol Hepatol Open Access 1(3): 00019. DOI: 10.15406/ghoa.2014.01.00019

6. Prieto M, Berenguer M, Rayon JM, Cordoba J, Arguello L, et al. (1999) High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. Hepatology 29(1): 250-256.

7. Berenguer M, Schuppan D (2013) Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol 58(5): 1028-1041.

8. Charlton M, Seaberg E, Wiesner R, Everhart J, Zetterman R, et al. (1998) Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology 28(3): 823-830.

9. Charton MR, Thompson A, Veldt BJ, Watt K, Tillmann H, et al. (2011) Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. Hepatology 53(1): 317-324.

10. Fukuhara T, Taketomi A, Motomura T, Okano S, Ninomiya A, et al. (2010) Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. Gastroenterology 139(5): 1577-1585.

11. Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, et al. (2000) Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology 32(4 Pt 1): 852-858.

12. Baron PW, Sindram D, Higdon D, Howell DN, Gottfried MR, et al. (2000) Prolonged rewarming time during allograft implantation predisposes to recurrent Hepatitis C infection after liver transplantation. Liver Transpl 6(4): 407-412.

13. Sheiner PA, Schwartz ME, Mor E, Schluger LK, Theise N, et al. (1995) Severe or multiple rejection episodes are associated with early recurrence of hepatitis C after orthotopic liver transplantation. Hepatology 21(1): 30-34.

14. Berenguer M, Aguila V, Prieto M, San Juan F, Rayon JM, et al. (2006) Effect of calcineurin inhibitors on survival and histologic disease severity in HCV-infected liver transplant recipients. Liver Transpl 12(5): 762-767.

15. Berenguer M, Aguila V, San Juan F, Benlloch S, Rubin A, et al. (2010) Effect of calcineurin inhibitors in the outcome of liver transplantation in hepatitis C virus-positive recipients. Transplantation 90(11): 1204-1209.

16. Cisneros L, Londono MC, Blasco C, Bataller R, Miquel R, et al. (2010) Hepatic stellate cell activation in liver transplant patients with hepatitis C recurrence and in non-transplanted patients with chronic hepatitis C. Liver transplantation 13(7): 1017-1027.

17. Asthana S, Toso C, Meeberg G, Bigam DL, Mason A, et al. (2011) The impact of sirolimus on hepatitis C recurrence after liver transplantation. Can J Gastroenterol 25(1): 28-34.

18. Rosen HR, Shackleton CR, Higa L, Graheik IM, Farmer DA, et al. (1997) Use of OKT3 is associated with early and severe recurrence of hepatitis C after liver transplantation. Am J Gastroenterol 92(9): 1453-1457.

19. Berenguer M (2008) Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin. J Hepatol 49(2): 274-287.

20. Terrault N (2008) Hepatitis C therapy before and after liver transplantation. Liver Transpl 14(Suppl 2): S58-S66.

21. Everson GT (2003) Treatment of Patients with Hepatitis C Virus on the Waiting List. Liver Transpl 9(11): S90-S94.

22. Everson G (2005) Should we treat patients with chronic hepatitis C on the waiting list? HEPATOLOGY 42(4): 456-462.

23. Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, et al. (2005) Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Hepatology 42(2): 255-262.

24. Forns X, Navasa M, Roder J (2004) Treatment of HCV infection in patients with advanced cirrhosis. Hepatology 40(2): 498.

25. Fried MW (2002) Side effects of therapy of hepatitis C and their management. Hepatology 36 (5 Suppl 1): S237-S244.

26. USFDA (2012) Serious skin reactions after combination treatment with the Hepatitis C drugs Incivek (telaprevir), peginterferon alfa, and ribavirin, FDA Drug Safety Communication. U.S. Food and Drug Administration, USA.

27. Poordad F, McConie J Jr, Bacon BR, Bruno S, Manns MP, et al. (2011) Boceprevir for untreated chronic HCV genotype 1 infection. N Eng J Med 364(13): 1195-1206.

28. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, et al. (2011) Telaprevir for previously untreated chronic hepatitis C virus infection. N Eng J Med 364(25): 2405-2416.

29. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, et al. (2011) Boceprevir for previously treated chronic hepatitis genotype 1 infection. N Eng J Med 364(13): 1207-1217.

30. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, et al. (2011) Telaprevir for retreatment of HCV infection. N Eng J Med 364(25): 2417-2428.

31. Bourliere M, Khaloun A, Wartelle-Bladou C, Oules V, Portal I, et al. (2012) Future treatment of patients with Hep C cirrhosis. Liver Int 32(Suppl 1): 113-119.

32. Crippin JS, Cashland T, Terrault N, Sheiner P, Charlton MR (2002) A pilot study of the tolerability and efficacy of antiviral therapy in HCV-infected patients awaiting liver transplantation. Liver Transpl 8(4): 350-355.

33. Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, et al. (2013) Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC)- NCT01514890. J Hepatol 59(3): 434-441.

34. Bourliere M, Khaloun A, Wartelle-Bladou C, Oules V, Portal I, et al. (2011) Chronic hepatitis C: treatments of the future. Clin Res Hepatol Gastroenterol 35 (Suppl 2): 584-595.

35. Fusco DN, Chung RT (2011) New protease inhibitors for HCV-help is on the way. J Hepatol 54(6): 1087-1089.

36. Wartelle-Bladou C, le Folgoc G, Bourliere M, Lecomte L (2012) Hepatitis C therapy in non-genotype 1 patients: the near future. J Viral Hepat 19(8): 525-536.

37. Zeuzem S, Berg T, Gane E, Ferracci P, Foster GR, et al. (2012) TMC435 in HCV genotype 1 patients who have failed previous pegylated interferon ribavirin treatment: Final SVR24 results of the ASPIRE trial. J Hepatol 56 (Suppl 2): S1-SZ.

38. Jacobson I, Dore G, Foster G, Fried MW, Rad M, et al. (2013) Simeprevir
Management of Hepatitis C in the Pre- and Post-Transplant Setting: Then and Now

52. Lawitz E, Coilly A, Roche B, Dumortier J, Leroy V, Botta-Fridlund D, et al. (2013) Simeprevir with peginterferon and ribavirin in treatment-naive HCV genotype 1 patients: Quest-2, a Randomized Phase III Trial. Journal of Hepatology 58: S564.

53. Verna EC, Burton JR, O'Leary JG, et al. (2013) A multicenter study of protease inhibitor-triple therapy in HCV-infected liver transplant recipients: report from the CRUSH-C group. 48th Annual Meeting of the European Association for the Study of the Liver (EASL 2013), Amsterdam, The Netherlands.

54. Fontana R, Qu R, Russo MW, Yoshida E, Brown K, Levitsky J (2013) Twice-Daily Telaprevir in Combination with Peginterferon Alfa-2a/Ribavirin in Genotype 1 HCV Liver Transplant Recipients: Interim Week 16 Calcineurin Inhibitor, Telaprevir and Ribavirin Pharmacokinetics from the Prospective Multicenter REFRESH Study. 64th Annual Meeting of ASLD, Wash DC.

55. Charlton MR, Gane EJ, Manns MP, Brown RS, Curry MP, et al. (2013) Sofosbuvir and ribavirin for the treatment of established recurrent hepatitis C infection after liver transplantation: Preliminary results of a prospective, multicenter study. Hepatology 58 (6 Suppl): 1378A.

56. Lawitz E, Lalezari J, Hassanein T, Kowdley K, Poordad F, et al. (2013) Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotype 1, 2, and 3 hepatitis C infection: a randomized, double-blind, phase 2 trial. Lancet Infect Dis 13(5): 401-408.

57. Saulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, et al. (2014) Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 370(3): 211-221.

58. Fontana RJ, Hughes EA, Bifano M, Appelman D, Dimitrova D, et al. (2013) Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. Am J Transplant 13(6): 1601-1605.

59. Bifano M, Adamczyk R, Hwang C, Kandoussi H, Marion A, et al. (2013) Daclatasvir pharmacokinetics in healthy subjects: no clinically-relevant drug-drug interactions with either cyclosporine or tacrolimus. Hepatology 58(4): 750A.

60. Kwo P, Manty P, Coakley E, Te H, Vargas H, et al. (2014) O114 results of the phase 2 study m12-999: interferon-free regimen of ABT-450/R/ABT-267+ ABT-333+ ribavirin in liver transplant recipients with recurrent hcv genotype 1 infection. Journal of Hepatology 60(1): S47.

61. Jacobson IM, Ghalib RH, Rodriguez-Torres M, Younossi ZM, Corregidor J, et al. (2013) SVR Results of a once-daily regimen of simeprevir (TMC455) plus sofosbuvir (GS-7977) with or without ribavirin in cirrhotic and noncirrhotic HCV genotype 1 treatment-naive and prior null-responder patients: The COSMOS study. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013), p. 1-5.

62. Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnu L, et al. (2007) Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: A Retrospective Study. Hepatology 45(3): 579-587.

63. Manns M, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, et al. (2001) Peginterferon alfa-2b + ribavirin compared with interferon alfa-2b + ribavirin for initial treatment of chronic hepatitis c: A Randomized trial. The Lancet 358(916): 958-965.

64. Kumar S (2013) Simeprevir administered once daily as part of combination therapy demonstrates sustained virologic response in treatment-naive and treatment-experienced genotype 1 chronic hepatitis c adult patients. Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013), USA.

65. Kumar S (2013)Sofosbuvir Taken Before or After Liver Transplant Reduces HCV Recurrence. Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013), USA.

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