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Severe Cholestatic Hepatitis C in Transplant Recipients: No Longer A Threat to Graft Survival

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Recurrence of hepatitis C virus (HCV) infection after liver transplantation is universal and happens within hours after transplantation[1,2]. The ensuing clinical manifestations of recurrent disease are quite variable but the most severe manifestation, termed cholestatic hepatitis, occurs early and aggressively. Historically, this was a dreaded entity, with all untreated patients experiencing graft loss within 2 years[3–7]. A poor understanding of the factors causing this presentation of recurrence coupled with a lack of effective therapies, added to the concern when this diagnosis was made. However, all of that is now in the past, with the availability of safe and highly effective direct antiviral agents (DAAs) transforming the natural history of cholestatic hepatitis.

The term fibrosing cholestatic hepatitis C is frequently used in the literature, borrowing from the histological entity first described in 1991 among patients transplanted for hepatitis B virus infection[8]. However, since fibrosis is less consistently seen with hepatitis C and is not a requirement for the diagnosis, the term cholestatic hepatitis C is more accurate and preferred. First described by Schulger and colleagues in 1996, the reported incidence of severe cholestatic hepatitis C is 2–15%, with the variability in part reflecting the lack of a consistent definition[3,4,9,10]. In 2003, an International Consensus Panel proposed the following diagnostic criteria[11]: (1) longer than 1 month post transplantation; (2) serum bilirubin level greater than 6 mg/dL; (3) serum alkaline phosphatase and gamma-glutamyltransferase levels greater than five times the upper limits of normal; (4) characteristic histology with ballooning of hepatocytes predominantly in the perivenular zone, paucity of inflammation, and variable degrees of cholangiolar proliferation without bile duct loss; (5) very high serum HCV RNA levels; and (6) absence of surgical biliary complications (normal cholangiogram) and hepatic artery thrombosis. More recently, Verna and colleagues suggested focusing on histopathology and proposed the following diagnostic criteria (at least three of four features on biopsy)[9]: (1) prominent ductular reaction resembling a biliary obstruction in the majority of portal tracts; (2) cholestasis (defined as

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canalicular bile plugs and/or intracellular bile pigment); (3) prominent hepatocyte ballooning with lobular disarray; and (4) any degree of periportal sinusoidal/pericellular fibrosis). Although the pathogenesis of severe cholestatic hepatitis C is largely unknown, this pattern of injury is thought to reflect the direct cytopathic effect of massive virus replication[12]. Since this histologic presentation is not described outside the setting of transplantation, donor and immunosuppressive factors are also likely of importance[13].

Historically, the therapeutic approach in patients with severe cholestatic hepatitis was to reduce immunosuppression and attempt viral eradication with antiviral therapy. While this recommendation sounds simple enough, its execution was quite complex. In early post-transplant, reducing immunosuppression brought the possibility of inciting concurrent rejection and treatment with peginterferon (peg-IFN) and ribavirin (RBV) was difficult and poorly tolerated among patients recently transplanted. Thus, success in the pre-DAA era was modest at best. In a systematic review of 35 reported cases of cholestatic hepatitis treated with peg-IFN-based therapy, 13 (37%) had a biochemical or virological response, whereas the others either died or required retransplantation[14]. Reports of a high rate of clinical relapse after treatment discontinuation lead some investigators to suggest indefinite treatment with peg-IFN and RBV in patients with cholestatic hepatitis[15].

Treatment outcomes began to improve with the approval of the first DAAs. Among nine post-transplant patients with cholestatic hepatitis treated with peg-IFN, RBV and a first-generation protease inhibitor (telaprevir or boceprevir) in the CRUSH-C consortium study[16], 4 (44%) achieved a sustained virological response (SVR) with 24–44 weeks of treatment. Fontana et al reported successful eradication of HCV after 24 week treatment with peg-IFN, RBV and daclatasvir (DCV) in a patient with severe recurrent cholestatic hepatitis C three months after her second transplant[17]. However, the safety and tolerability of peg-IFN and ribavirin remains a significant challenge in the treatment of these patients.

The major advance occurred was when all oral DAA combinations became available. From single case reports to large series, a consistent message is emerging – severe cholestatic hepatitis is a treatable condition and SVR is attainable in the vast majority of patients [17–25] (Table). For many patients with severe cholestatic hepatitis, early compassionate access programs provided life-saving therapy and much of what we have learned about the safety and efficacy of DAA combination therapy in cholestatic hepatitis comes from these programs. Forns et al published a series of 104 transplanted patients with severe recurrent hepatitis C, including 10 patients with severe cholestatic hepatitis, who received sofosbuvir (SOF) and ribavirin (RBV) with/without peginterferon via compassionate access[21]. Of the 92 patients with SVR results, patients with acute or early severe recurrence had a higher SVR rate (73%) than those with recurrent cirrhosis (43%). Among the ten patients with a clinical diagnosis of cholestatic hepatitis, 8 achieved SVR12 (80%). Additionally, ascites, hepatic encephalopathy and indices of liver synthetic function improved in a greater proportion of patients with early recurrent hepatitis (69%) than of patients with decompensated cirrhosis (45%). This was the first study to suggest that patients with severe cholestatic hepatitis treated with DAA combination therapy have a better clinical prognosis than patients with recurrent hepatitis C with advanced fibrosis.

The study of Leroy and al, published in this issue of Clinical Gastroenterology and Hepatology[25], adds to the evolving story on treatment outcomes in patients with severe cholestatic hepatitis. The authors describe the natural history of 23 patients with well-characterized cholestatic hepatitis C who were treated via a French compassionate access program with SOF, RBV and Peg-IFNα (8 patients) or SOF, DCV and RBV (15 patients) for 24 weeks. Impressively, all patients were alive without re-transplantation at 36 weeks after treatment initiation and SVR12 was achieved in 22 patients (96%). Moreover, the rapidity of improvement in liver-related symptoms and laboratory values is notable. While eight patients (35%) started treatment with ascites, only one patient had ascites 36 weeks after treatment initiation. There was also a drastic decrease in median bilirubin levels from 122.0 μmol/L (43.0–191.0) to 11.8 μmol/L (9.0–20.0) at the end of follow-up. Moreover, the therapy was generally well tolerated, although anemia was frequent and 78% required use of growth factors and 52% blood transfusions. The latter reflects the toxicity of ribavirin in this setting and the need for ribavirin-free DAA combinations.

Included among the treatment patients in the report from Leroy and colleagues were 4 patients with HCV-HIV coinfection. While a small number of patients, this warrants special emphasis, as the natural history of recurrent HCV disease post-transplant in HCV-HIV coinfected patients is more accelerated, cholestatic hepatitis more frequent and graft losses higher than patients with HCV monoinfection[26]. Three of the four patients achieved SVR suggesting that severe cholestatic disease is manageable in most coinfected transplant patients also. While the drug-drug interactions between DAAs, immunosuppressives and antiretroviral drugs add to the complexity of treating coinfected transplant recipients, the high efficacy of SOF plus RBV and SOF/DCV and RBV seen in this study are encouraging.

Looking forward, the greater use of antivirals to achieve SVR among wait-listed patients will reduce the incidence of cholestatic hepatitis post-transplantation. However, the number of safe DAA treatment options currently available for those with advanced decompensated disease is limited[27] so delaying antiviral therapy to the post-transplant period may be the preferred antiviral strategy, especially as this allows for the use of anti-HCV positive donors. For transplant recipients with recurrent HCV infection, cholestatic hepatitis will remain a possible complication but the reported experience with DAA combinations (SOF/RBV, SOF/DCV, SOF-ledipasvir ±RBV) indicates that clinical resolution and viral eradication will be achievable in the majority of treated patients and that cholestatic hepatitis will no longer be the threat to graft survival that it once was.

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Abbreviations

HCV	Hepatitis C virus

DAAs	Direct antiviral agents
MELD	Model for end-stage liver disease
RBV	Ribavirin
SOF	Sofosbuvir
DCV	Daclatasvir
SVR	Sustained virologic response

Reference

1. Ramirez S, Perez-Del-Pulgar S, Forns X. Virology and pathogenesis of hepatitis C virus recurrence. Liver Transpl. 2008; 14(Suppl 2):S27–S35. [PubMed: 18825723]
2. Garcia-Retortillo M, Forns X, Feliu A, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatology. 2002; 35:680–687. [PubMed: 11870384]
3. Satapathy SK, Sclair S, Fiel MI, Del Rio Martin J, Schiano T. Clinical characterization of patients developing histologically-proven fibrosing cholestatic hepatitis C post-liver transplantation. Hepatol Res. 2011; 41:328–339. [PubMed: 21426450]
4. Schluger LK, Sheiner PA, Thung SN, et al. Severe recurrent cholestatic hepatitis C following orthotopic liver transplantation. Hepatology. 1996; 23:971–976. [PubMed: 8621177]
5. Dickson RC, Caldwell SH, Ishitani MB, et al. Clinical and histologic patterns of early graft failure due to recurrnet hepatitis C in four patients after liver transplantation. Transplantation. 1996; 61:701–705. [PubMed: 8607170]
6. Radecke K, Fruhauf NR, Miller M, et al. Outcome after orthotopic liver transplantation in five HIV-infected patients with virus hepatitis-induced cirrhosis. Liver Int. 2005; 25:101–108. [PubMed: 15698406]
7. Prachalias AA, Pozniak A, Taylor C, et al. Liver transplantation in adults coinfected with HIV. Transplantation. 2001; 72:1684–1688. [PubMed: 11726833]
8. Davies SE, Portmann BC, O'Grady JG, et al. Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis. Hepatology. 1991; 13:150–157. [PubMed: 1988336]
9. Verna EC, Abdelmessih R, Salomao MA, Lefkowitch J, Moreira RK, Brown RS Jr. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. Liver Transpl. 2013; 19:78–88. [PubMed: 23081888]
10. Cimsit B, Assis D, Caldwell C, et al. Successful treatment of fibrosing cholestatic hepatitis after liver transplantation. Transplant Proc. 2011; 43:905–908. [PubMed: 21486625]
11. Wiesner RH, Sorrell M, Villamil F. International Liver Transplantation Society Expert P. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl. 2003; 9:S1–S9. [PubMed: 14586888]
12. Demetris AJ. Evolution of hepatitis C virus in liver allografts. Liver Transpl. 2009; 15(Suppl 2):S35–S41. [PubMed: 19876940]
13. Duarte-Rojo A, Budhraja V, Veldt BJ, et al. Interleukin-28B and fibrosing cholestatic hepatitis in posttransplant hepatitis C: a case-control study and literature review. Liver Transpl. 2013; 19:1311–1317. [PubMed: 24039107]
14. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. Liver Transpl. 2010; 16:1228–1235. [PubMed: 21031537]
15. Gopal DV, Rosen HR. Duration of antiviral therapy for cholestatic HCV recurrence may need to be indefinite. Liver Transpl. 2003; 9:348–353. [PubMed: 12682884]

16. Verna EC, Saxena V, Burton JR Jr, et al. Telaprevir- and Boceprevir-Based Triple Therapy for Hepatitis C in Liver Transplant Recipients With Advanced Recurrent Disease: A Multicenter Study. Transplantation. 2015
17. Fontana RJ, Hughes EA, Appelman H, Hindes R, Dimitrova D, Bifano M. Case report of successful peginterferon, ribavirin, and daclatasvir therapy for recurrent cholestatic hepatitis C after liver retransplantation. Liver Transpl. 2012; 18:1053–1059. [PubMed: 22706796]
18. Fontana RJ, Hughes EA, Bifano M, et al. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. Am J Transplant. 2013; 13:1601–1605. [PubMed: 23593993]
19. Ueda Y, Kaido T, Hatano E, Ohtsuru S, Uemoto S. Safe and effective treatment with daclatasvir and asunaprevir in a liver transplant recipient with severe cholestatic hepatitis C. Hepatol Res. 2015
20. Kim B, Trivedi A, Thung SN, Grewal P. Case report of successful treatment of fibrosing cholestatic hepatitis C with sofosbuvir and ribavirin after liver transplantation. Semin Liver Dis. 2014; 34:108–112. [PubMed: 24782264]
21. Forns X, Charlton M, Denning J, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology. 2015; 61:1485–1494. [PubMed: 25557906]
22. Pellicelli AM, Montalbano M, Lionetti R, et al. Sofosbuvir plus daclatasvir for post-transplant recurrent hepatitis C: potent antiviral activity but no clinical benefit if treatment is given late. Dig Liver Dis. 2014; 46:923–927. [PubMed: 24997638]
23. Pungpapong S, Aqel B, Leise M, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. Hepatology. 2015; 61:1880–1886. [PubMed: 25722203]
24. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients with Advanced Liver Disease. Gastroenterology. 2015
25. Leroy V, Dumortier J, Coilly A, et al. Efficacy of Sofosbuvir and Daclatasvir in Patients with Fibrosing Cholestatic Hepatitis C After Liver Transplantation. Clin Gastroenterol Hepatol. 2015
26. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. Liver Transpl. 2012; 18:716–726. [PubMed: 22328294]
27. Panel AIHG. Hepatitis C Guidance: AASLD-IDSA Recommendations for Testing, Managing, and Treating Adults Infected with Hepatitis C Virus. Hepatology. 2015

Table

Summary of DAA Combination Therapy for Severe Cholestatic Hepatitis*

Author, Year, Ref	N	Median time from LT to treatment (months)	DAA Combination Therapy	Duration Therapy (weeks)	SVR12 Rate	Survival
Pellicelli, 2014[22]	3	--	SOF + DCV +/− RBV	24	N/A End of treatment response: 67%	67%
Pungpapong, 2015[23]	13	--	SOF + Simeprevir + RBV	12	100%	100%
Forns, 2015[21]	10	--	SOF + RBV +/− peg-IFN	24–48	80%	100%
Charlton, 2015[24]	6	13.2 (12-wk treatment arm) 3.6 (24-wk treatment arm)	Ledipasvir + SOF + RBV	12 or 24	100%	100%
Leroy, 2015[25]	23	11.1 (SOF + RBV + peg-IFN) 4.9 (SOF + DCV + RBV)	SOF + RBV + Peg-IFN (N=8) SOF + DCV + RBV (N=15)	24	96%	100%

*Excludes single case reports

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