Ledipasvir and sofosbuvir for treatment of post- renal transplant hepatitis C infection: A case report with review of literature

R. Jha, R. Fatima, S. Lakhtakia[1], A. Jha[2], P. Srikant, G. Narayan

Department of Nephrology, Medwin Hospital, [1]Department of Medical Gastroenterology, Asian Institute of Gastroenterology, [2]Department of Medicine, Mediciti Medical College, Hyderabad, Telangana, India

ABSTRACT

Liver disease due to hepatitis C infection in renal transplant recipients is difficult to treat and often associated with reduced patient survival. A 43-year-old male, a renal allograft recipient, presented at 6 years follow-up with significant weight loss over 3 months. He was detected to have new onset diabetes mellitus together with hepatitis C virus (HCV) infection (genotype 1). His HCV load remained high despite the change of immuno-suppression from tacrolimus to cyclosporine. A decision to treat with a new anti-viral combination of ledipasvir and sofosbuvir for 12 weeks was taken. Within 3 weeks, his raised serum transaminases levels normalized and viral load became undetectable. At the end of 16 weeks, he continues to do well with normal renal function, has sustained remission from hepatitis C infection and resolution of diabetes.

Key words: Hepatitis C infection, ledipasvir, renal transplant, sofosbuvir

Introduction

Treatment options for hepatitis C virus (HCV) infection in renal transplant (RTx) patients are limited.[1,2] The conventional treatment of interferon (IFN) injection with ribavirin carries the risk of allograft rejection. Conversely, not treating for HCV is associated with increased morbidity and mortality due to progressive liver dysfunction, infections, malignancy, vasculitis, glomerulonephritis, and new onset diabetes.[3] The availability of second generation oral anti-viral drugs has opened new avenues for HCV treatment.[4] Although used successfully in liver transplant situation, there is no available literature for their use in RTx patient. We share our early experience of a RTx patient with HCV infection treated successfully with combination pill of sofosbuvir (SOF) and ledipasvir (LDV) (Harvoni), heralding a new era of safe, IFN - free, oral, anti-HCV therapy

Case Report

A 43-year-old male renal allograft recipient, presented at the sixth year follow up with significant weight loss of 6kg over 3 months. Prior to renal transplantation he was hypertensive, nondiabetic and HCV negative (confirmed by standard ELISA and polymerase chain reaction [PCR] test). His native kidney disease was chronic glomerulonephritis. He underwent living related donor RTx from haplo-identical male (cousin). Induction therapy included basiliximab 2 doses (20 mg each) followed by triple drug immuno-suppression (prednisolone, tacrolimus, mycophenolate mofetil [MMF]) He received two units blood transfusion

Address for correspondence:
Dr. R. Jha,
Department of Nephrology, Medwin Hospital, Nampally,
Hyderabad - 500 001, Telangana, India.
E-mail: rtnjha@yahoo.com

Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.163432

How to cite this article: Jha R, Fatima R, Lakhtakia S, Jha A, Srikant P, Narayan G. Ledipasvir and sofosbuvir for treatment of post- renal transplant hepatitis C infection: A case report withreview of literature. Indian J Nephrol 2016;26:216-9.

in the peritransplant period. His posttransplant period was uneventful with normal renal function until the recent complaint. He was receiving prednisolone 5 mg daily, MMF500 mg thrice daily, and tacrolimus 1 mg twice daily. His other medications included nifedipine 20 mg thrice daily, metoprolol 50 mg once daily and calcium carbonate 500 mg twice daily. His clinical evaluation was unremarkable. Laboratory evaluation showed *de novo* new onset diabetes mellitus after transplant (fasting blood glucose 225 mg/dl, hemoglobin A1c 11.9), elevated liver enzymes (aspartate transaminase 89 IU/L [normal <40], alanine transaminase 159 IU/L [normal <40], gamma glutamyl transferase 150 IU/L, biliburin 1 mg%, serum albumin 4 g/dl), normal renal functions (serum creatinine 0.9 mg%), normal hemogram, and chest X-ray. Furthermore, the evaluation showed HBsAg negative, anti-HCV serology positive status due to HCV genotype 1 with high viral load (10,800,000 IU/ml). There was no evidence of cirrhosis, portal hypertension or ascites on ultrasound abdomen. Upper gastrointestinal endoscopy was normal. Liver biopsy was not performed. His immunotherapy was modified from tacrolimus to cyclosporine (50 mg BD). Diabetes was initially controlled with insulin and later he was switched to oral sitagliptin-metformin combination. His serum transaminases level remained elevated over next 9 months with persistent high HCV load (106,074,000 IU/ml). The patient was counseled about the risk of allograft rejection with existing anti-HCV therapy, and lack of treatment guidelines for using oral new anti-viral agents in RTx situation. However, with recent treatment success with newer oral anti-viral agents in non-RTx situation, the patient consented to take oral anti-viral therapy under closed supervision. He received the fixed-dose combination of LDV and SOF (Harvoni), manufactured by Gilead Sciences. for next 12 weeks. At 3 weeks (after starting treatment), his serum transaminase levels normalized and HCV viral load became undetectable. His renal function remained stable. Doppler ultrasound and radionuclide study with technetium-99m-diethylene-triamine-pentaacetate were normal. His serum cyclosporine trough level was in the acceptable range (110.2 ng/ml whole blood at 3 weeks while baseline was 95 ng/ml by liquid chromatography-tandem mass spectrometry normal range 80–150 on long-term). He continues to do clinically well at four months posttreatment In addition, after completion of oral anti-viral therapy he is off anti-diabetic treatment with maintained euglycemia and normal liver functions.

Discussion

Liver disease is an important cause of morbidity and mortality in RTx recipients, especially with HCV infection. Abnormal liver functions test are reported in 7–24% of RTx recipients, with liver failure as the cause of death in 8–28% of long-term survivors.[5] Liver disease in RTx patient may be due to viral infections (hepatitis B virus or HCV, Epstein-Barr virus, or cytomegalovirus), drugs (azathioprine or cyclosporine), iron overload (hemosiderosis) or alcohol abuse.

HCV infection in immuno-suppressed RTx recipient is associated with significant morbidity and mortality.[6,7] Most HCV serology positive RTx recipients have persistent HCV viremia. Patients with HCV-positive status prior to transplantation have increased risk of posttransplant liver disease with a relative risk (RR) of 5.0.[8] One large meta-analysis, that included 6365 HCV positive patients reported increased risk for death (RR 1.79) and allograft failure (RR 1.56).[9] HCV infection additionally causes heightened immuno-suppression thereby increasing the risk of sepsis in the initial years post-RTx and liver disease in later years that progresses more rapidly compared to the nontransplant situation to chronic hepatitis, cirrhosis, and liver cancer.[10] Conversely, acute presentation due to HCV is rare. HCV infection is also associated with increased risk for new onset diabetes after transplantation (NODAT), *de novo* glomerulonephritis and mixed cryoglobulinemia-related vasculitis that may lead to graft loss or recipient death.[3] Interestingly, the present case highlights that the patient who developed NODAT associated with HCV infection may have a collateral benefit of getting cured of diabetes with control of HCV infection.

Efforts to minimize the incidence of post-RTx HCV infection must focus on viral screening of both donors and recipients using sensitive methods in the pretransplant stage. Third generation ELISA serology for the detection of HCV has high sensitivity (>98%). Positive ELISA test suggests that either past inactive infection or current active transmissible infection. The latter is confirmed by a gold standard PCR test that detects HCV RNA antigen, which should be done in all patients prior to transplant. The index patient was negative for HCV by ELISA and PCR in pre-RTx evaluation. He probably acquired HCV infection from blood transfusions (tested negative by ELISA) received in peritransplant period though a remote possibility of missed HCV infection in pretransplant evaluation exists.[10] The latter may occur in patients who have intermittent viremia from the sequestered virus in the liver or peripheral mononuclear cells leading to negative serum HCV status.

The standard care for the patients with HCV genotype 1 infection in non-RTx scenario is pegylated IFN plus

ribavirin with newer direct acting anti-viral protease inhibitor (boceprevir or telaprevir) for 48 weeks.[11] The overall sustained virological response (SVR) rate in patients infected with HCV genotype 1 is poor (<50%) compared to genotype 2 or 3 (approximately 75–80%) more so in patients on dialysis (nearly one-third).[2,11] Current treatment option approved for patients ineligible to receive INF in HCV genotype 1 infection is 24 weeks of SOF and ribavirin.[12] There are no standard guidelines for RTx recipients with chronic HCV infection. RTx is a contraindication to IFN therapy due to its limited efficacy, increased risk of acute rejection, high cost, and significant side effects.[2,11] However, IFN mono-therapy is to be considered in kidney transplant recipients with HCV infection having fibrosing cholestatic hepatitis or life-threatening vasculitis.[11] Ribavirin in the post-RTx state does not produce sustained virologic response despite lowering of transaminase level.

Current clinical strategy in the post-RTx HCV infection is manipulation of immunosuppressive therapy (minimizing corticosteroid, avoidance of anti-lymphocyte antibody, and to replace Tacrolimus with Cyclosporine).[13] However, there is an urgent need for newer anti-HCV therapies with greater safety and efficacy than IFN and ribavirin in RTx patient. The drugs used as "add-on oral therapy" in HCV treatment include ribavarine, telaprevir, boceprevir, or simeprevir in different combinations. The advent of newer second generation anti-virals like SOF -LDV, ombitasvir-paritaprevir plus dasabuvir, daclatasvir-asunaprevir, and simeprevir-SOF has widened the therapeutic options with reported SVR above 90%.[4] The novel oral anti-viral agents are likely to cause a paradigm shift in the treatment of HCV infection in post-RTx state by simplifying current therapy of shorter duration and also eliminating the need for response guided therapeutic approach. The choice between these agents depends primarily on the potential for drug interactions and drug toxicity. The combination therapies are preferred as they provide better viral suppression than mono-therapy with less chance of viral escape based on complementary resistance profiles.[14] There is no additional benefit by extension of the duration of treatment to even 24 weeks. Addition of ribavirin to a LDV-SOF combination increases toxicity without any additional efficacy.[15]

LDV-SOF combination has favorable adverse effect profile (common side effects rated as mild and not leading to drug discontinuation like fatigue, headache, nausea, diarrhea, and insomnia reported in 10–20%), minimal drug interactions, and easy to administer (single pill daily). Our patient did not complain of any side effect. LDV is an inhibitor of the HCV NS5A protein that is required for viral replication, postreplication assembly, and secretion. It has potent anti-viral activity against HCV genotypes 1a and 1b. SOF, a nucleotide pro-drug and an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, acts as a chain terminator. Sofosobuvir, the backbone of the new standard of care for HCV infection, offers a number of potential benefits such as high rates of sustained virologic response, high barrier to resistance, tolerability, pan-genotype efficacy (HCV genotype 1–6), need for shortened duration of treatment, usefulness in cirrhosis, human immunodeficiency virus co-infection and liver transplantation. SOF (400 mg) in combination with LDV (90 mg) (Harvoni) has been proven to be efficacious, tolerable and safe in series of clinical trials, both in treatment-naïve and treatment-experienced patients with 12–24 weeks of therapy (depending presence or absence of cirrhosis, treatment experience, and genotype) with high sustained viral response.[14,15] The index RTx patient with a very high viral load without cirrhosis showed a remarkable response as early as 3 weeks after therapy. Shorter duration for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pretreatment HCV RNA of <6 million IU/ml. Both SOF and LDV are substrates of P-glycoprotein inducers (like rifampicin) with implication for potential drug interactions but it does not demonstrate significant drug interactions with immunosuppressant drugs. We also found no drug interaction in our patient, particularly with cyclosporine.

Conclusion

Necessity is the mother of invention. The development of IFN free oral anti-HCV therapy may be a major breakthrough in anti-HCV management in RTx patient. The dual drug combination therapy appears to be an important arrow in our quiver now for targeting HCV infection in high-risk RTx. Such combination therapy may shorten and simplify treatment regimens even in the post-RTx scenario ushering a new era of safer, simpler and more effective therapy.[2,14,15] However, the utility versus the risk of such new therapy has to be scrutinized carefully by studies involving a sizeable cohort of RTx patients having long-term follow-up for reliable assessment of such therapeutic intervention.

Acknowledgment

We thank our colleagues and staff of Nephrology.

Financial support and sponsorship

Medwin Hospital, Nampally, Hyderabad, Andhra Pradesh, India.

Conflicts of interest

There are no conflicts of interest.

References

1. Fabrizi F, Martin P. Management of hepatitis B and C virus infection before and after renal transplantation. Curr Opin Organ Transplant 2006;11:583-8.
2. Bunchorntavakul C, Maneerattanaporn M, Chavalitdhamrong D. Management of patients with hepatitis C infection and renal disease. World J Hepatol 2015;7:213-25.
3. Sandri AM, Elewa U, Poterucha JJ, Fervenza FC. Treatment of hepatitis C-mediated glomerular disease. Nephron Clin Pract 2011;119:c121-30.
4. Kwo PY, Badshah MB. New hepatitis C virus therapies: Drug classes and metabolism, drug interactions relevant in the transplant settings, drug options in decompensated cirrhosis, and drug options in end-stage renal disease. Curr Opin Organ Transplant 2015;20:235-41.
5. Pereira BJ, Levey AS. Hepatitis C virus infection in dialysis and renal transplantation. Kidney Int 1997;51:981-99.
6. Morales JM, Campistol JM. Transplantation in the patient with hepatitis C. J Am Soc Nephrol 2000;11:1343-53.
7. Fabrizi F, Martin P, Ponticelli C. Hepatitis C virus infection and renal transplantation. Am J Kidney Dis 2001;38:919-34.
8. Periera BJ, Wright TL, Schmid CH, Levey AS. The impact of pretransplantation hepatitis C infection on the outcome of renal transplantation. Transplantation 1995;60:799-805.
9. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Hepatitis C virus antibody status and survival after renal transplantation: Meta-analysis of observational studies. Am J Transplant 2005;5:1452-61.
10. Rubin RH. Infectious disease complications of renal transplantation. Kidney Int 1993;44:221-36.
11. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Int Suppl 2008;73: S1-99.
12. Osinusi A, Meissner EG, Lee YJ, Bon D, Heytens L, Nelson A, *et al.* Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: A randomized clinical trial. JAMA 2013;310:804-11.
13. Watashi K, Hijikata M, Hosaka M, Yamaji M, Shimotohno K. Cyclosporin A suppresses replication of hepatitis C virus genome in cultured hepatocytes. Hepatology 2003;38:1282-8.
14. Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Subramanian GM, *et al.* Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014;146:736-43.e1.
15. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, *et al.* Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): An open-label, randomised, phase 2 trial. Lancet 2014;383:515-23.