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Perspective of antiviral therapeutics for hepatitis C after liver transplantation

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Core tip: Management of hepatitis C virus (HCV) recurrence after liver transplantation used to be a bothering issue due mostly to the interferon-based therapy. Current available data from treatment of chronic HCV infection shows promising results of interferon-free, or even ribavirin-free, pan-genotypic, all oral medications will soon reform the treatment of HCV recurrence after liver transplantation.

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Abstract

Hepatitis C virus (HCV) almost recurs after liver transplantation for HCV-related liver cirrhosis or hepatocellular carcinoma. Management of HCV recurrence after liver transplantation is challenging because the traditional interferon-based therapy is often patient-intolerable and inducing cytopenia, and dose reduction is needed. The response rate in liver recipients is inferior to those of chronic HCV infection. About 5 percent of liver recipients receiving interferon-based therapy would develop immune-mediated graft injury and may need retransplantation. Recent advances of anti-HCV therapy for chronic HCV infection has evolutionary changing the schema from interferon-based, to interferon-free, and even to ribavirin -free, all oral combinations for pan-genotypes. Management of HCV recurrence after liver transplantation is currently evolving too and promising results will soon come to the stage. This "fast-track" concise review focuses on the issues relevant to HCV recurrence after liver transplantation and provides up-to-date information of the trend of the management. A real-world case demonstration of management was presented here to illustrate the potential complications of anti-HCV therapy after liver transplantation.

INTRODUCTION

Hepatitis C-related liver cirrhosis or hepatocellular carcinoma is the main indication of liver transplantation worldwide[1-4]. Almost all recipients experiences post-transplant recurrence of hepatitis C virus (HCV) and some degrees of long-term graft injury[5,6]. Although hepatitis C is a potentially curable disease because it is caused by an RNA flavivirus with 6 major genotypes[4], and, unlike hepatitis B virus which integrates its DNA into host DNA genome and causes viral clearance difficult, therapeutic outcomes were inferior in liver recipients compared to patients of chronic HCV infection[7].

Ongoing evolutionary positive results in "general" (non-recipient) population shed promising lights on HCV liver recipients who are still struggling to suffer from the recurrence. The aim of this concise review is to illustrate the current and, more importantly, future pictures of the anti-HCV therapeutics after liver transplantation for non-hepatologists by summarizing a great varieties of reviews

Table 1 Category, mode of action and major side-effects of anti-hepatitis C virus therapy

Category	Specific target	Mechanism of action	Major side-effect
Interferon α	Host hepatocytes and immune cells	Enhance host immune response	Flu-like symptoms
Ribavirin (nucleoside inhibitor)	Nucleoside guanosine analogue	Stop viral RNA synthesis and viral mRNA capping Enhance interferon response	Cytopenia
DAA			
Protease inhibitor (NS3 inhibitor or NS3/4A inhibitor)	NS 3 serine protease ± NS4A cofactor	Inhibit cleavage of the HCV proteins from the polyprecursor	Transfusion-dependent anemia; drug interaction with calcineurin inhibitors
HCV polymerase inhibitor (NS 5B inhibitor)	NS 5B protein (RNA-dependent RNA polymerase)	Inhibit HCV replication	Minimal
NS 5A replication complex inhibitor	NS 5A protein (protein for viral RNA replication and inteferon-resistance)	Stop viral RNA replication	Minimal

DAA: Direct acting antiviral agent; NS: Non-structural; HCV: Hepatitis C virus.

and articles. Detailed or extensive dissections of single agents are beyond the scope of this fast-track review and will be suggested to references.

COURSES OF HEPATITIS C AFTER LIVER TRANSPLANTATION-CONSIDER MORE THAN JUST VIRAL LOAD IN LIVER RECIPIENTS

Early experiences showed that after liver transplantation for HCV-related cirrhosis, persistent HCV infection can cause severe graft damage, and such damage is more frequent in patients infected with HCV genotype 1b than with other genotypes[8].

As more experiences accumulated around the world, the natural history of HCV is accelerated after liver transplantation with 20%-40% progressing to cirrhosis within 5 years[9-12]. Evidence of markers and risk factors, including clinical, serum, histopathological, or donor-related, to early predict this group of patients is summarized well in Howell *et al*[5] and Mariño *et al*[13] review and is still being identified. Crespo *et al*[6] proposed simplified algorithm, combining risk factors (old donors, female recipients, diabetes mellitus, cytomegalovirus infection and corticosteroid boluses) and non-invasive liver stiffness measurement, for management of HCV recurrence after liver transplantation and further consolidated the timing for antiviral intervention.

The primary goal in this scenario is prevention of graft loss from fibrosis progression[12]. Viral load does not correspond to graft injury[14]. Clinicians should note that progression of fibrosis is occasionally observed even in patients who responded to treatment; in these cases, progression may be related to other factors, such as smoldering rejection, nonalcoholic steatohepatitis, other graft-related issues, or older donor or patient age[14]. About 5% of liver recipients receiving interferon-based regimens would develop rejection or graft fibrosis, in the absence of HCV[14]. They could be related to interferon-induced innate alloimmune response or fluctuation of immunosuppressant levels *via* drug interactions[15-18].

Once graft injury progresses irreversibly, either through fibrosis due to HCV recurrence or through therapeutic-induced, immune-mediated injury, retransplantation is often the only option of treatment[19,20]. Patient and graft survival rates after retransplantation in these circumstances, however, are inferior to those after primary liver transplantation[19] although it seems no different compared to those of retransplantation due to other reasons[20].

TRENDS OF ANTI-HCV THERAPY RELEVANT TO LIVER TRANSPLANTATION- NEW INSIGHTS TOWARD THE NEAR FUTURE

HCV was first isolated and identified in 1989[21]. Lai *et al*[22] pioneer study found that interferon-based therapy increased the sustained virologic response and thereafter was considered as the standard of care for HCV treatment. Interferon-based therapy augments the innate immune response to cure the virus[23]. Ribavirin synergistically increase the interferon effect through NK cell activation[24]. As the 3D crystalized structure of HCV was identified, more and more targets disclosed and large upcoming amounts of new drugs designed to achieve better effect[25,26]. Non-structural (NS)3/4A protease inhibitors were added to the interferon-based regimen and increased the sustained virological response (SVR) further[25].

The effective therapy against chronic HCV infection has improved dramatically recently, with expected SVR rates of near 75% in all previously untreated patients and the current treatment guidelines was summarized by Gane *et al*[12].

Recently, NS 5B polymerase inhibitor further raised the response rate substantially and open the era of interferon-free, all oral, regimens[25]. NS 5B and NS 5A fixed, once daily combination further suggest the possibility of ribavirin-free regimens in the near future[27,28]. Shorter treatment course and pan-genotypic response, in previous treatment failure or cirrhotic patients make anti-HCV treatment revolutionary[27-29]. The evolutionary trend of

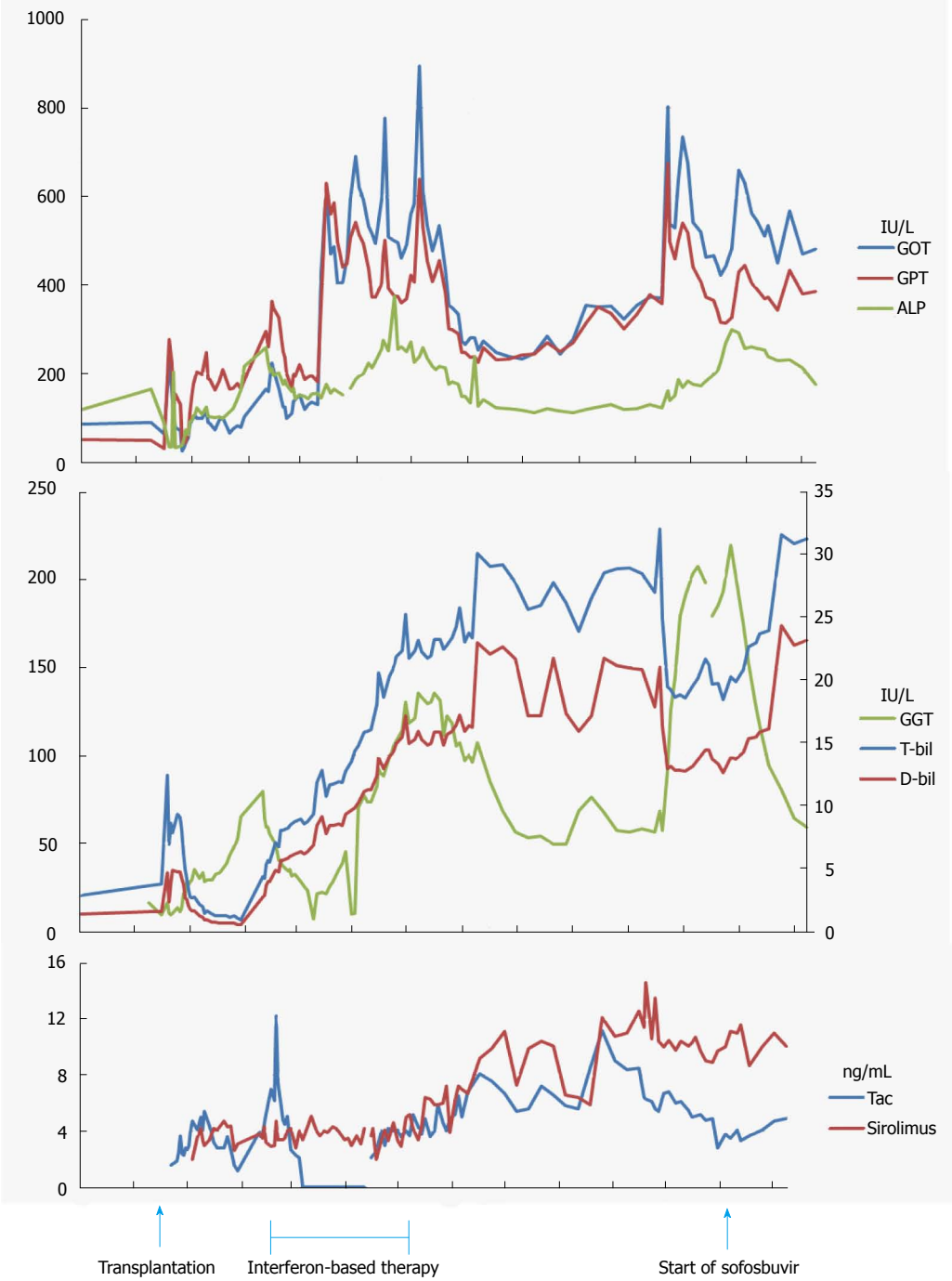

Figure 1 Post-transplant course of a liver recipient with hepatitis C recurrence.

anti-HCV therapy was nicely presented in Heim's work[25].

Table 1 summarized the major anti-HCV therapeutic agents, mode of actions, and major side effects. High cost will be the major issue of anti-HCV therapy in the world instead[30]. In the future, the indication for ribavirin would be limited only to non-nucleotide-based combinations or failure of other oral combination[7,31].

ANTI-HCV THERAPY AFTER LIVER TRANSPLANTATION-THE REAL WORLD

Interferon-based regimens after liver transplantation achieved 30% SVR in liver recipients, with higher rates achievable in patients with non-1 genotypes[32,33]. A lot of HCV liver recipients, however, are rejected for the regimens from the start or early in the course of treatment because of the side effect intolerance. In fact, the most negative predictor for viral response is lack of tolerability from pegylated interferon/ribavirin-more than 80% of patients dose reduce and almost 30% cease therapy because of adverse effects[12]. These results highlight the critical need for better tolerated and more efficacious HCV therapies for HCV transplant recipients[12].

Interferon-based, NS 3A/4A added regimens after

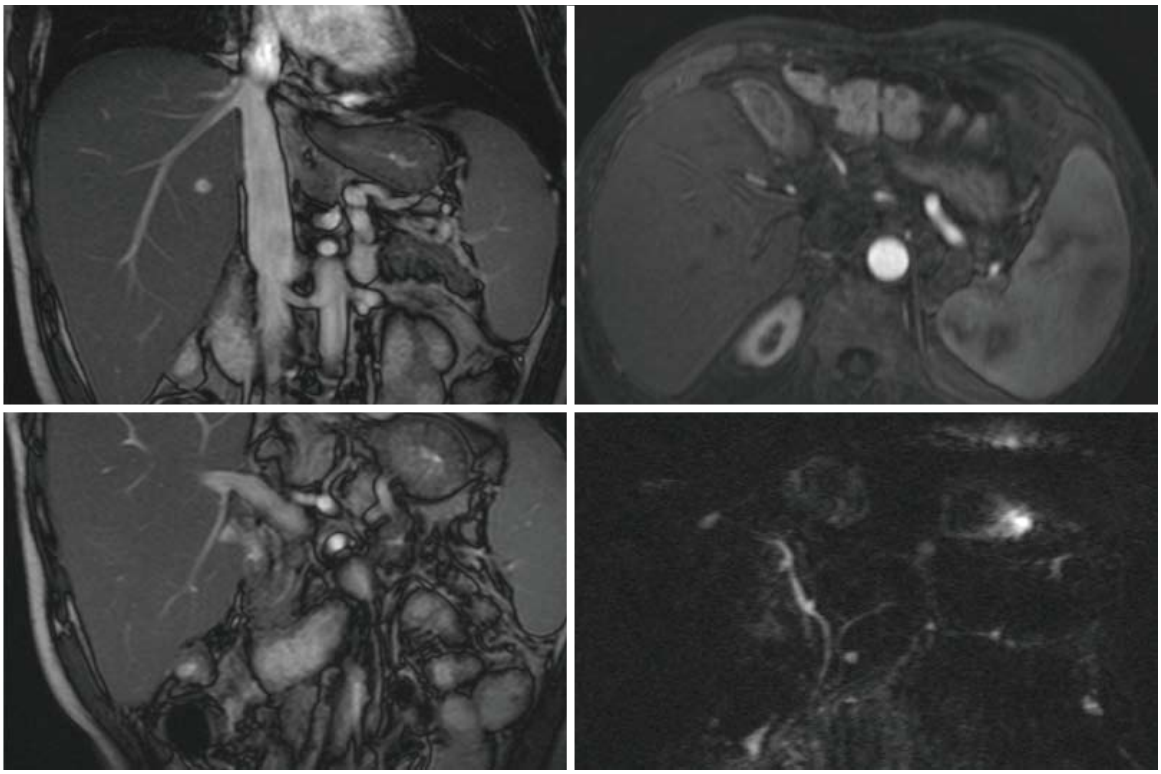

Figure 2 Magnetic resonance imaging screening for liver graft vascular or biliary complications.

liver transplantation could be further increased the SVR to 50%[34]. Discontinuation rates were still observed high and over one third of patients need blood transfusion[12]. In addition, antiviral therapy utilizing boceprevir in liver transplant recipients requires close monitoring of cyclosporine (5-fold) or tacrolimus (70-fold increase) due to the enzyme inhibition of the cytochrome P450 3A[12].

A case report of the HCV liver recipient with good virological response using NS 5B inhibitor show promise of translating the success in "general" HCV population to HCV liver recipients[35]. Sarkar *et al*[31] reported preliminary, multi-center, promising results of sofosbuvir and ribavirin for post-transplant HCV recurrence (more than 80% had HCV genotype 1) in the Liver Meeting 2013. They found a rapidly decline of HCV after starting therapy, and over 70% of 40 recipients had SVR 4 wk after completing treatment[36,37]. Only 2 (5%) had side effects that led to treatment discontinuation[36,37]. These studies had actively formulating the future all-oral treatment regimens in HCV liver recipients.

REAL-WORLD CASE DEMONSTRATION

A 59 year-old man, received liver transplantation for HCV-related liver cirrhosis, was referred for prolonged and progressive jaundice since 2 mo following liver transplantation. Serial liver biopsies showed chronic hepatitis C and serum viral load was 5.8×10^6 IU/mL with the genotype 1B. Interferon-based therapy was initiated soon but lasted for 3 mo because of patient intolerance. The viral load was 1.3×10^4 IU/mL at this time. Jaundice, however, was progressive. Laboratory data of liver profiles were shown in Figure 1. Image survey showed no evidence of vascular or biliary complications (Figure 2). Immunosuppressant regimens were tacrolimus-based initially, withdrawal transiently for the threat of drug-related cholestasis, and followed by re-initiation. The serum levels of immunosuppressant (tacrolimus and sirolimus) were shown in Figure 1. Interferon-based therapy with add-in sofosbuvir were restarted 9 mo after liver transplantation. Ribavirin and sofosbuvir were used 3 wk later without interferon because of the patient intolerance. Serum viral load dropped dramatically to undetectable 3 mo after the use of sofosbuvir, 11 mo after transplantation and remained thereafter. The latter serial liver biopsies (from 5 mo to 11 mo after liver transplantation), however, showed first acute rejection, and chronic rejection later. Steroid bolus therapy was not responsive. Liver retransplantation was suggested.

CONCLUSION

In summary, with the rapid advances of anti-viral therapy in HCV hepatitis, the prognosis of HCV liver recipients is expected to improve greatly once the all oral, interferon-free, ribavirin-free regimens come to the stage of the standard of care with reasonable cost.

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