Hepatitis C Virus: Antiviral Therapy in Wait-Listed Patients

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Recurrent infection with hepatitis C virus (HCV) after liver transplantation (LT) is universal in patients who are viremic at the time of transplantation. Recurrent HCV is associated with reduced graft survival and increased patient mortality.^{1,2} Current antiviral treatments for established posttransplant recurrence are characterized by low rates of virological clearance, poor tolerability, cytopenias, infections, drug interactions with immunosuppressants, and a risk of allograft rejection. In addition, allografts are often significantly damaged by HCV by the time of the initiation of antiviral treatment.³ Preventing the recurrence of HCV infection is desirable.

Pretransplant antiviral therapy for wait-listed patients is one strategy for preventing allograft reinfection by HCV. In some cases, achieving a sustained virological response (SVR) might stabilize or reverse the liver disease and potentially prevent the need for LT. However, for most wait-listed patients, the primary goal is rendering the blood free of HCV at the time of transplantation to achieve posttransplant viral clearance, which is defined as HCV RNA being undetectable 12 weeks or more after transplantation [posttransplant viral response (pTVR)]. Achieving pTVR eliminates the risk of recurrence and should preserve graft function, increase graft survival, and improve patient outcomes and survival.⁴⁻⁷ Despite the potential benefits, the effectiveness of pretransplant treatment is dependent on the potency and tolerability of the antiviral regimen and the severity of the underlying liver disease.

Interferon-Based Treatment

Current treatment options are limited. The standard of care for HCV genotype 1 (GT1) is peginterferon (PEG)/ribavirin

(RBV) plus either telaprevir or boceprevir (triple therapy).⁸⁻¹² For non-1 genotypes, the standard of care is PEG/RBV alone.¹³⁻¹⁵ These treatments are less effective in patients with cirrhosis because of reduced virological responses and poor tolerability.

Patients with HCV on the waiting list exhibit a wide range of disease severity, which affects selection for treatment. Interferon-related side effects, adverse reactions, and serious adverse events occur with greater frequency and severity in patients with decompensated cirrhosis. Patients with high Model for End-Stage Liver Disease (MELD) scores or clinical complications such as ascites, variceal hemorrhage, and encephalopathy are poor candidates because they are at increased risk for serious infections, hepatic decompensation, and even death. Thus, interferon-based treatment is limited to patients with MELD scores < 18 and lesser hepatic impairment, such as potential recipients of living donor grafts and potential recipients of deceased donor grafts with MELD upgrades for hepatocellular carcinoma.

The Low Accelerating Dose Regimen-Adult-to-Adult Living Donor Liver Transplantation Study (LADR-A2ALL) was a randomized controlled trial of PEG/RBV treatment.¹⁶ Candidates included HCV patients with either potential living donors or MELD upgrades for hepatocellular carcinoma. Among the treated GT1/genotype 4 (GT4)/genotype 6 (GT6) patients, 23 of 30 received a transplant, and 22% of these patients achieved pTVR. Among the treated genotype 2 (GT2)/genotype 3 (GT3) patients, 21 of 29 received a transplant, and 29% of these patients achieved pTVR. The likelihood of achieving pTVR was related to the duration of treatment: 50% of the patients who received the treatment for >16 weeks achieved pTVR ($P = 0.01$; Fig. 1). The

Abbreviations: 1st, first-generation drug; 2nd, later generation drug; 5aI, inhibitor of nonstructural 5A protein; DAA, direct-acting antiviral; GT1, genotype 1; GT2, genotype 2; GT3, genotype 3; GT4, genotype 4; GT5, genotype 5; GT6, genotype 6; HCV, hepatitis C virus; LADR-A2ALL, Low Accelerating Dose Regimen-Adult-to-Adult Living Donor Liver Transplantation Study; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NI, nucleos(t)ide-based inhibitor of nonstructural 5B polymerase; PEG, peginterferon; PI, inhibitor of nonstructural 3/4A protease; pTVR, posttransplant viral response; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response

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% HCV RNA negative

FIGURE 1. Results of pretransplant treatment with the low accelerating dose regimen in LADR-A2ALL.¹⁶ The likelihood of pTVR was related to the duration of treatment: the pTVR rate was 50% for patients receiving greater than 16 weeks of PEG/RBV. At LTx refers to the HCV RNA status at the time of LT; pTVR indicates undetectable HCV RNA 12 weeks or more after transplantation.

overall pTVR rate reported in this study (25%) was similar to the rates reported by Everson et al.¹⁷ (26%), Forns et al.¹⁸ (23%), and Carrión et al.¹⁹ (23%). In all of these studies, some treated patients experienced serious, even life-threatening adverse events (mainly infections). Antibiotic prophylaxis to prevent spontaneous bacterial peritonitis is recommended. Patients with cirrhosis frequently have baseline cytopenias that worsen during treatment. In LADR-A2ALL, 75% of the treated patients required an erythropoietin analogue or granulocyte colony-stimulating factor, alone or in combination.¹⁶ Eltrombopag can raise platelet counts and potentially improve the chances for SVR, but it carries a risk for portal vein thrombosis and hepatic decompensation.²⁰

Patients infected with HCV GT1 currently have the option to be treated with triple therapy. The A New Direction in HCV Care: A Study of Treatment-Naïve Hepatitis C Patients with Telaprevir (ADVANCE),⁹ Illustrating the Effects of Combination Therapy with Telaprevir (ILLUMINATE),¹¹ and Serine Protease Inhibitor Therapy-2 (SPRINT-2) studies¹⁰

showed that patients with cirrhosis have much higher rates of SVR when they are treated with triple therapy versus PEG/RBV. SVR with triple therapy is also predicted by the responsiveness to interferon. Patients who have interleukin-28b polymorphism CC (versus CT or TT), a greater than 1 log₁₀ drop in HCV RNA during the lead-in with PEG/RBV, or a relapse response to prior PEG/RBV are more likely to achieve SVR when they are treated with triple therapy.⁸⁻¹²

There is limited information regarding the use of triple therapy in wait-listed patients. Verna et al.²¹ presented results for 28 HCV GT1 patients awaiting LT. Nine (32%) discontinued treatment because of adverse events, a null response, relapse, hepatic decompensation, or death. Rates for achieving undetectable HCV RNA were 50%, 71%, and 80% at weeks 4, 8, and 12, respectively. Eight patients (28%) underwent LT, and six of them had undetectable HCV RNA after transplantation (pTVR rate = 75%). One patient with pTVR received only 3 weeks of triple therapy. Among the transplant patients, 75% were treatment-experienced, and 88% had hepatocellular carcinoma. There were two deaths: one before transplantation (due to an unknown cause) and one after transplantation (due to sepsis).

This early experience suggests that pretransplant treatment using triple therapy may be more effective than PEG/RBV alone in achieving pTVR in patients with an HCV GT1 infection. However, the treatment is complicated by serious side effects, adverse events, and potentially life-threatening complications. Anemia is a major problem requiring RBV dose reduction, the use of erythropoietin analogues, and blood transfusions.

Emerging Drugs and Interferon-Free Treatment

The next wave of antiviral drugs for HCV may include sofosbuvir (SOF; nonstructural 5b polymerase inhibitor),

TABLE 1: Speculations Regarding Future Drug Regimens for Pretransplant Treatment, Timelines, and Potential or Expected SVR or pTVR Rates, Treatment Durations, and Severity of Side Effects

Genotype	Year	Treatment Options	SVR or pTVR Rate (%)	Optimum Duration of Treatment (%)			Severity of Side Effects
				<8 Weeks	8-16 Weeks	>16 Weeks	
GT2 or GT3	2013	PEG/RBV	29-50	—	—	100	++++
	≥2013	RBV-NI	>65	20	80	—	+
GT1a or GT1b	2013	PEG/RBV	20-25	—	—	100	+++++
	2013	PEG/RBV + PI-1st	40	—	80	20	+++++
	≥2013	PEG/RBV + PI-2nd	55	—	80	20	+++
	≥2014	PEG/RBV-5al	55	—	80	20	+++
	≥2014	PEG/RBV-NI	>60	—	100	—	++
	≥2014	RBV-NI	>55	—	100	—	+
	≥2014	Multi-DAA	>60	20	80	—	++
	≥2014	5al + PI-2nd	>60	20	80	—	+
GT1b	≥2014	5al + PI-2nd	>60	20	80	—	++
GT1a	>2014	PEG/RBV + 5al + PI-2nd	>60	20	80	—	++

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Abbreviations: 1st, first-generation drug; 2nd, later generation drug; 5al, inhibitor of nonstructural 5A protein; NI, nucleos(t)ide-based inhibitor of nonstructural 5B polymerase; PI, inhibitor of nonstructural 3/4A protease. + shows severity of side effects, where + is minimum and +++++ is maximum side effects.

FIGURE 2. Impact of cirrhosis on SVR with SOF-based treatment.^{23,27} Cirrhosis reduces the likelihood of achieving SVR during SOF treatment. This effect of cirrhosis is true whether patients are treatment-naïve (GT1 and GT3); interferon-ineligible, intolerant, or unwilling (GT3); or treatment-experienced (GT2 and GT3). The negative impact of cirrhosis on SVR can be at least partially reversed by an extension of the duration of SOF/RBV treatment (GT2 and GT3). P stands for PEG/RBV, % SVR 12 stands for sustained viral response at 12 weeks post treatment. Weeks indicated in the X-axis are duration of total treatment.

simeprevir (nonstructural 3/4a protease inhibitor), faldaprevir (nonstructural 3/4a protease inhibitor), and daclatasvir (nonstructural 5a protein inhibitor). These drugs have greater potency, a lower potential for drug-drug interactions, once daily dosing, a shorter duration of therapy, and fewer side effects. The increased tolerability should expand the pool of pretransplant patients who could be candidates for treatment²² (Table 1).

GT1 [and GT4, Genotype 5 (GT5), and GT6]. The initial use of SOF, simeprevir, faldaprevir, or daclatasvir in patients infected with HCV GT1, GT4, GT5, or GT6 is likely to be in combination with PEG/RBV. In a trial of treatment-naïve patients, 17% of whom had cirrhosis, 12 weeks of SOF/PEG/RBV achieved an SVR rate of 92% in patients without cirrhosis and an SVR rate of 80% in patients with cirrhosis²³ (Fig. 2). In studies of simeprevir/PEG/RBV, 85% to 93% of patients had a rapid virological response and qualified for a reduced treatment duration of 24 weeks. Overall, 79% to 81% of patients achieved SVR despite F3/F4 fibrosis in 22% to 31% of the cases (Medivir press releases, December 2012). Clearly, the new drugs offer advantages over both telaprevir and boceprevir: higher potency, ease of dosing, and fewer side effects. However, virological responses may be further impaired in sicker wait-listed patients who have more advanced liver disease.

Preliminary results with multi direct-acting antivirals (DAAs), interferon-free regimens in HCV GT1 patients without cirrhosis are very encouraging.²⁴⁻²⁶ SVR rates approach 100% with few, if any, side effects or adverse reactions.

Promising combinations, with or without RBV, include SOF/ledipasvir, SOF/daclatasvir, SOF/simeprevir, daclatasvir/asunaprevir, daclatasvir/asunaprevir/BMS-791325, and ABT-450/r/ABT-333/ABT-267. We must emphasize that none of these regimens has been adequately tested in patients with cirrhosis (particularly decompensated cirrhosis) or in patients on the waiting list for LT.

GT2 and GT3. Three phase 3 trials have examined the efficacy of SOF/RBV in patients infected with HCV GT2 or GT3^{23,27} (Fig. 2). HCV RNA declines rapidly and is undetectable by week 4 in nearly all patients. Treatment failures are primarily due to relapse without evidence of viral resistance. The reported side effects have been those associated with RBV. Treatment-naïve patients with HCV GT2 (even those with cirrhosis) achieved an SVR rate > 90% with 12 weeks of treatment. Treatment-experienced HCV GT2 patients with cirrhosis benefited from an extension of the treatment from 12 to 16 weeks (the SVR rate improved from 60% to 78%). Treatment-experienced HCV GT3 patients with cirrhosis demonstrated the greatest improvement in SVR when the treatment duration was increased from 12 to 16 weeks (the SVR rate increased from 19% to 61%).

This simple all-oral regimen would seem to be ideal as a pretransplant treatment for preventing recurrent infection of the allograft. However, the metabolic derangements and portosystemic shunting of cirrhosis could alter the pharmacokinetics and bioavailability of these drugs and impair efficacy. We anxiously await results from studies of interferon-

free combinations of DAAs in cirrhosis and advanced liver disease.

In summary, the era of DAAs for HCV has expanded treatment options for the wait-listed patient. Rates of pTVR after pretransplant treatment have improved with current triple therapy, but the management of side effects and complications remains challenging. Future regimens

incorporating interferon-free, multi-DAA treatments should improve the effectiveness and tolerability of pre-transplant treatment. ■

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