

Management of hepatitis C infection in the era of direct-acting antiviral therapy

L H Zain¹ and T Sungkar^{1*}

¹Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, University of Sumatera Utara, Indonesia

*Corresponding author: taufik.sungkar@usu.ac.id

Abstract. Hepatitis C viral infection globally affects millions of people and commonly results in debilitating complications and mortality. Initial mainstay therapy consisted of pegylated interferon α (pegIFN α) with additional ribavirin that showed unsatisfactory cure rate, common side effects and complicated dosing, contributing to high discontinuation rate. Over the last few years, newer antivirals have been extensively studied, that are Direct-Acting Antivirals (DAAs). Specifically targeting viral protein mainly during replication phase, DAAs showed greater cure rate (commonly measured as sustained virologic response), improved safety profile and shorter treatment duration compared to traditional interferon-ribavirin therapy. Current guidelines have also included Interferon-free, often ribavirin-free, DAAs combinations that suggest promising outcomes. The current review highlights development of rapidly growing hepatitis C treatment including DAAs recommendations.

1. Introduction

To date, hepatitis C viral infection remains to be a global health challenge. Nearly 180 millions of people were infected worldwide, with reported debilitating complications as high as 25% including cirrhosis and hepatocellular carcinoma.[1] Worldwide, at least six major genomes (GT1-6) has been identified with genotype 1 (GT1) being the most common (49.1%) followed by genotype 3 (GT3) as the second most common (17.9%).[2] One parameter to mark successful HCV eradications has been the rate of sustained virologic response (SVR). HCV treatment is thus directed to improve SVR, prevent complications and to eradicate the virus, of which has been a challenging, but immensely growing task.[3]

For many years, standard therapy consists of pegylated interferon α (pegIFN α) with additional ribavirin (RBV). In terms of SVR, this early era therapy showed poor rates and varied greatly among genomes. The SVR was 40% for GT1 and GT4.[4] Along with its unsatisfactory cure rate, reported side effects were also common thus promoting discontinuation rate. Newer regimens have been developed to improve cure rate, increase tolerability thus hopefully prevent complications. One of which is direct-acting antivirals (DAAs) agents that specifically target proteins responsible for specific viral pathogenesis. Later approach include interferon-ribavirin-DAAs regimen, also known as triple therapy, which further investigation showed several downfalls. In the current DAA era, recent recommendations approve interferon-free, some are ribavirin-free, DAAs combination, which mainly suggested according to its genotypes.[3]



2. Previous Interferon-Ribavirin Therapy

Up until 2011, the combination of pegylated interferon α (pegIFN α) with ribavirin (RBV) has been used as a standard regimen for HCV, that consisted of 24-48 weeks of treatment duration.[5] Treatment outcome varied greatly among genomes. Despite being the most common, GT1 remains the most difficult to control, with SVR of only 40% following completion of 48 weeks standard therapy.[6]

3. Development of Direct-Acting Antiviral (DAA) – first generation

First generation NS3/4A PIs include telaprevir (TVR) and boceprevir (BOC) that had been approved in 2011 for treating GT1 infection. TVR and BOC promote viral clearance through inhibiting NS3/4A protease which responsible for viral replication.[7]

To prevent viral resistance, which has been an inevitable issue in drugs discovery, first generation DAA (either TVR or BOC) was added to the traditional PEG-IFN/RBV which also known as ‘triple therapy’.[8] This approach greatly improve SVR of up to 75%, however observed effective in GT1 only. Other than exclusively potent for GT1, side effects were also common that includes anemia, rash, and fatigue contributing to high drop off rate. Dosing was also complicated, being three times daily taken with fatty meals, as well as potentially altering drug-to-drug interactions especially in patients with comorbidities requiring multiple medications. Cirrhotic patients also did not respond well to therapy, with poorer SVR and more frequent side effects.[9]

4. Newer Agents of DAAs

4.1. NS3/4A protease inhibitors

To improve performance and tolerability of first generation NS3/4A protease inhibitor (PI), newer generation PI has been developed that includes Simeprevir, Paritaprevir, Grazoprevir and the latter addition Asunaprevir, Voxileprevir, and Glecaprevir. This newer generation performs better in terms of efficacy especially within GT1, induces fewer side effects and allows lower therapeutic dosing. Simeprevir is newer first generation NS3/4A protease inhibitor, showing 80-81% SVR for GT1 infection.[10]

Second generation NS3/4A PI includes Grazoprevir. In vitro, Grazoprevir affects all genomes. As part of triple therapy, it showed SVR of 89-93% in non-cirrhotic GT1 infection.[11]

4.2. NS5A inhibitors

NS5A inhibitors include the pangenotypic Daclatasvir, and the more genome-specific Ledipasvir, Elbasvir, Ombitasvir, Velpatasvir, and Odalasvir. As part of triple therapy, Daclatasvir showed effectiveness in GT1 and GT4 infection.[12] Daclatasvir has also currently been studied in combination with other DAAs as a pangenotypic treatment, that is effective against all genome, hence simplifying treatment.[8]

4.3. NS5B inhibitors

The aforementioned combinations include NS5B inhibitors, namely sofosbuvir and dasabuvir. Viral NS5B mediates RNA synthesis in viral replication phase. Sofosbuvir showed pangenotypic activity in vitro and in trials.[13] Remarkable SVR has also been shown in multiple trials when Sofosbuvir was given as part of triple therapy.[38-40] It also showed effectivity in GT2, 3 and 4 when ribavirin was added (interferon-free). Highest SVR was observed in GT2 and GT4 infection. Following 12 weeks therapy of Sofosbuvir and Ribavirin, around 86-97% GT2 patients achieved SVR. This high SVR however was not observed for GT3 and GT4 when 12 weeks treatment duration was applied. Longer duration study, the VALENCE trial, showed 85% SVR in GT3 (compared to 30% for 12-weeks treatment and 62% for 16-weeks treatment).[14] Trials investigating GT4 also showed 68-77% SVR in 12-weeks therapy and 90-93% in 24-weeks therapy. Phase III trial suggested for Sofosbuvir and Ribavirin combination, longer treatment duration is needed for GT3 and GT4 to improve SVR.[15]

5. Current DAAs recommendations

To date, at least six major genotypes with several subtypes have been identified.[20] Each possesses its own unique structure that demands different regimens approach. Table 1 and 2 includes current recommendations based on European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) of HCV treatment according to cirrhotic and treatment status.[8] The following section highlights current recommended combinations that have been developed specific to each genotype.

Table 1. Current recommendations according to EASL and AASLD in HCV patients without cirrhosis.

Without cirrhosis				
Genotype	Treatment-naïve	Duration	Treatment-experienced	Duration
1	SOF/LDV	8-12 Weeks	SOF/LDV $\pm$ RBV	12 Weeks
	SOF/VEL	12 Weeks	SOF/VEL	12 Weeks
	RTV-PTV/OBV/DSV $\pm$ RBV	8-12 Weeks	RTV-PTV/OBV/DSV $\pm$ RBV	12 Weeks
	GZR/EBR	12 Weeks	GZR/EBR	12 Weeks
	SOF + DCV	12 Weeks	SOF + DCV $\pm$ RBV	12 Weeks
	SOF + SMV	12 Weeks	SOF + SMV	12 Weeks
2	SOF/VEL	12 Weeks	SOF/VEL	12 Weeks
	SOF + DCV	12 Weeks	SOF + DCV	12 Weeks
3	SOF/VEL	12 Weeks	SOF/VEL $\pm$ RBV	12 Weeks
	SOF + DCV	12 Weeks	SOF + DCV $\pm$ RBV	12 Weeks
4	SOF/LDV	12 Weeks	SOF/LDV $\pm$ RBV	12 Weeks
	SOF/VEL	12 Weeks	SOF/VEL	12 Weeks
	RTV-PTV/OBV + RBV	12 Weeks	RTV-PTV/OBV + RBV	12 Weeks
	GZR/EBR	12 Weeks	GZR/EBR	12 Weeks
	SOF + DCV	12 Weeks	SOF + DCV $\pm$ RBV	12 Weeks
	SOF + SMV	12 Weeks	SOF + SMV $\pm$ RBV	12 Weeks
5/6	SOF/LDV	12 Weeks	SOF/LDV $\pm$ RBV	12 Weeks
	SOF/VEL	12 Weeks	SOF/VEL	12 Weeks
	SOF + DCV	12 Weeks	SOF + DCV $\pm$ RBV	12 Weeks

Table 2. Current recommendations according to EASL and AASLD in HCV patients with cirrhosis.

With cirrhosis				
Genotype	Compensated: Treatment-naïve/ treatment-experienced	Duration	Decompensated	Duration
1	SOF/LDV $\pm$ RBV	12 Weeks	SOF/LDV + RBV	12 Weeks
	SOF/VEL	12 Weeks	SOF/VEL + RBV	12 Weeks
	RTV-PTV/OBV/DSV $\pm$ RBV	12/24 Weeks		
	GZR/EBR	12 Weeks		
	SOF + DCV $\pm$ RBV	12 Weeks	SOF + DCV + RBV	12 Weeks
	SOF + SMV	12 Weeks		
2	SOF/VEL	12 Weeks	SOF/VEL + RBV	12 Weeks
	SOF + DCV	12 Weeks	SOF + DCV + RBV	12 Weeks
3	SOF/VEL	12 Weeks	SOF/VEL + RBV	24 Weeks
	SOF + DCV + RBV	24 Weeks	SOF + DCV + RBV	24 Weeks
4	SOF/LDV $\pm$ RBV	12 Weeks	SOF/LDV + RBV	12 Weeks
	SOF/VEL	12 Weeks	SOF/VEL + RBV	12 Weeks
	RTV-PTV/OBV + RBV	12 Weeks		
	GZR/EBR	12 Weeks		
	SOF + DCV $\pm$ RBV	12 Weeks	SOF + DCV + RBV	12 Weeks
	SOF + SMV $\pm$ RBV	12 Weeks		
5/6	SOF/LDV $\pm$ RBV	12 Weeks	SOF/LDV + RBV	12 Weeks
	SOF/VEL	12 Weeks	SOF/VEL + RBV	12 Weeks
	SOF + DCV $\pm$ RBV	12 Weeks	SOF + DCV + RBV	12 Weeks

6. Special Population

6.1. Hepatitis C viral infection in chronic kidney disease

Current management of HCV in patients with renal impairment includes combination of DAAs, often interferon-free. According to EASL recommendation in 2016, patients with mild to moderately impaired renal functions (eGFR ≥ 30 ml/min/1.73 m²) requires no dose adjustment to several regimens, including SOF/RBV, SOF/LDV, SOF/VEL, RTV-PTV/OMB/DSV, GZR/EBR, SOF/DCV or SOF/SMV. Hence to be treated in a similar fashion as to non-CKD cases.[8]

With a number of DAAs being excreted and accumulated in kidneys special considerations need to be made in severe renal impairment. In patients with eGFR < 30 ml/min/1.73 m²), including stage 4 and 5 CKD or hemodialysis patients, the use of the renally excreted sofosbuvir is not recommended. The TARGET-2.0 study showed progressive renal dysfunction in patients receiving sofosbuvir regimen. Thus, sofosbuvir-free regimens should be preferred in ESRD and hemodialysis patients. The RUBY-1 study confirmed the use of sofosbuvir-free regimen, that was ritonavir-boosted paritaprevir, ombitasvir and dasabuvir in GT1 infection, of which 65% received once daily 200 mg ribavirin vs 35% did not. Following 12 weeks of treatment endpoint, SVR showed 90%.[16] The C-SURFER trial also studied sofosbuvir-free, grazoprevir and elbasvir regimen for 12 weeks, which showed similarly high 94% SVR.[17]

6.2. Co-infection of hepatitis C and HIV

Regimens for treatment of co-infection VHC-HIV are generally similar to those in VHC monoinfection, DAA-based therapy according to genotype. Therapy using DAA regimens can be done regardless of CD4. In PHOTON-1 study, combination of sofosbuvir and ribavirin for 12 and 24 weeks in genotype 1, 2, and 3 naïve patients, obtained 76% SVR12 for genotype 1 (24 weeks), 88% for genotype 2 (12 weeks), and 67% for genotype 3 (12 weeks); whereas for patients failing therapy, obtained 92% SVR12 for genotype 2 and 94% for genotype 3 with a duration of therapy for 24 weeks. A similar therapy was given in the PHOTON-2 study. in naïve patients, combination of sofosbuvir and ribavirin for 12 weeks (genotypes 2) and 24 weeks for other genotypes gave SVR12 for 85% for genotype 1, 89% for genotype 2, 91% for genotype 3, and 84% for genotype 4; whereas in patients failing therapy, a combination of 24-week therapy gave 83% SVR12 in genotype 2 and 86% in genotype 3. Combination of elbasvir/grazoprevir therapy for 12 weeks were also shown to have satisfactory SVR12 in VHC-HIV coinfecting patients, 94% for genotypes 1a, 96% for genotype 1b and genotype 4, 94% in non-cirrhotic patients, and 100% in cirrhotic patients.[18]

7. Conclusions

The last few years has shown rapidly growing discoveries in hepatitis C treatment. Previous interferon-ribavirin-first generation DAAs has not been a favorable options, leading to further investigation of DAAs combinations. DAAs combination has shown great SVR, some even achieved complete SVR. Recent trials have been directed to pangenotypic approach in an attempt to simplify treatment as 'one-size-fits-all'. Results of ongoing trials are to be awaited; in the meantime, current recommendations have provided genome-specific treatment options with high cure rates and safety profile.

References

- [1] Seeff L B 2002 Natural history of chronic hepatitis C *Hepatology* **36** S35-S46
- [2] Petruzzello A, Marigliano S, Loquercio G, *et al.* 2016 Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes *World J. Gastroenterol.* **22**(34) 7824–40
- [3] Jazwinski A and Muir A 2011 Direct-acting antiviral medications for chronic hepatitis C virus infection *Gastroenterol. Hepatol.* **3**(7)

- [4] Feld J J, Kowdley K V, Coakley E, *et al.* 2014 Treatment of HCV with ABT-450/r- ombitasvir and dasabuvir with ribavirin *N. Engl. J. Med.* **370**(17) 1594-603
- [5] Ghany M G, Strader D B, Thomas D L and Seeff L B 2009 Diagnosis, management, and treatment of hepatitis C: an update *Hepatology* **49** 1335-74
- [6] Mc Hutchison J G, Lawitz E J, Shiffman M L, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection *N. Engl. J. Med.* **361** 580-93
- [7] European Association for Study of Liver 2015 EASL recommendations on treatment of hepatitis C *J. Hepatol.* **63**(1) 199–236
- [8] Burstow N, Mohamed Z, Gomaa A, *et al.* 2017 Hepatitis C treatment: where are we now? *Int. J. Gen. Med.* 10
- [9] Price J C, Murphy R C, Shvachko V A, *et al.* 2014 Effectiveness of telaprevir and boceprevir triple therapy for patients with hepatitis C virus infection in a large integrated care setting *Dig. Dis. Sci.* **59**(12) 3043–52
- [10] Manns M, Marcellin P, Poordad F, *et al.* 2014 Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial *Lancet* **384**(9941) 414–26
- [11] Manns M P, Vierling J M, Bacon B R, *et al.* 2014 The combination of MK-5172, peginterferon, and ribavirin is effective in treatment naïve patients with hepatitis C virus genotype 1 infection without cirrhosis *Gastroenterology* **147**(2) 366–76
- [12] Hézode C, Hirschfield G M, Ghesquiere W, *et al.* 2015 Daclatasvir plus peginterferon alfa and ribavirin for treatment-naïve chronic hepatitis C genotype 1 or 4 infection: a randomized study *Gut* **64**(6) 948–56
- [13] Lam A M, Murakami E, Espiritu C, *et al.* 2010 PSI-7851, a pronucleotide of beta-D-2 ϵ -deoxy-2 ϵ -fluoro-2 ϵ -C-methyluridine monophosphate, is a potent and pan-genotype inhibitor of hepatitis C virus replication *Antimicrob. Agents Chemother.* **54**(8) 3187–96
- [14] Zeuzem S, Dusheiko G M, Salupere R, *et al.* 2014 Sofosbuvir and ribavirin in HCV genotypes 2 and 3 *N. Engl. J. Med.* **370**(21) 1993–2001
- [15] Ruane P J, Ain D, Stryker R, *et al.* 2015 Sofosbuvir plus ribavirin for the treatment of chronic genotype 4 hepatitis C virus infection in patients of Egyptian ancestry *J. Hepatol.* **62**(5) 1040–6
- [16] Pockros P J, Reddy K R, Mantry P S, Cohen E, Bennett M, Sulkowski M S, *et al.* 2016 Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease *Gastroenterology* **150** 1590–8
- [17] Roth D, Nelson D R, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, *et al.* 2015 Grazoprevir plus elbasvir in treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study *Lancet* 3861537–45
- [18] Perhimpunan Peneliti Hati Indonesia 2017 Penatalaksanaan hepatitis C pada populasi khusus (Konsensus nasional penatalaksanaan hepatitis C di Indonesia) 86-11