



SHORT REVIEW

New Perspectives of HCV Infection: Focus on New Treatment Agents and Comorbidity Status, a Short Review

Huang Yu-Fen and Su Hui-Chen*

Department of Pharmacy, Chi Mei Hospital, Tainan, Taiwan

*Corresponding authors: Su Hui-Chen, Department of Pharmacy, Chi Mei Hospital, Taiwan, Tel: +886-6-281-2811, E-mail: michael.maggil@gmail.com



Abstract

Chronic hepatitis C (CHC) is one of the main leading causes of mortality associated with liver disease worldwide. Different predominant modes of transmission in the local area play an important role for the disease burden. Several cofactors are identified to accelerate the disease progression. Besides, several comorbidities are common in patients with CHC and also have poor response to the traditional combination of pegylated interferon and ribavirin (PegIFN/RBV) treatment. The treatment of CHC has been evolved rapidly, the traditional treatment of choice - PegIFN/RBV lasts more than a decade but the cure rate remains unsatisfied and shows heterogeneous response in various patient groups. In addition, considerable patients are intolerable to adverse reactions of PegIFN/RBV. The newly developed IFN-free regimens, oral direct antiviral agents (DAAs), lead to high SVR, short treatment duration and enhance tolerability. Also, the treatment of DAAs have been grown since 2011 persistently. The new generations of DAAs improved cure rate, tolerability and lead to more convenient administration. Some special populations, who are difficultly treated with PegIFN/RBV therapy, can also benefit from the new DAAs. There are some concerns still warranted in DAAs therapy, including drug-drug interactions between DAAs and co-medication for the comorbidity, severe renal impairment and decompensated liver disease, co-infection with HIV/HCV and HBV/HCV. Generally, cure of CHC become more possible but there are some aspects provided for clinical health caregivers for better DAAs management.

Keywords

Hepatitis C (HCV), Chronic hepatitis C (CHC), Direct-antiviral agent (DAA), Comorbidity, HIV/HCV coinfection, HBV/HCV coinfection, Severe renal impairment, Decompensated liver disease

Abbreviations

HCV: Hepatitis C; CHC: Chronic Hepatitis C; PWID: People Who Inject Drugs; HCC: Hepatocellular Carcinoma; PegIFN: Pegylated Interferon; RBV: Ribavirin; DAA: Direct Antiviral Agent; SVR: Sustained Virological Response

Current Global Epidemiology of Chronic Hepatitis C Infection

Chronic hepatitis C (CHC) infection remains a substantial public health problem affecting 71 million individuals in the world [1]. Although Hepatitis C (HCV) is found worldwide, there are large prevalence variations in different regions that reflect different endemic modes of transmission in the local areas. Sharing drug-injection equipment is more frequent in developed countries; whereas, unsafe injections and health care exposures are the predominant mode of transmissions in developing countries [2]. It was estimated that higher rate of HCV infection located in the Eastern Mediterranean Region, European Region, followed by African Region, and South-East Asia Region [3]. Because of common contributors as blood-borne transmission and unsafe sexual behavior, HCV epidemics can be concentrated in certain key populations, such as people who inject drugs (PWID) and HIV-infected men who have sex with men (MSM) [4-6]. The injection drug use was the leading cause of new HCV infections [2] and related to several outbreaks of acute HCV infections in younger age group [6]. Among the PWID, 65% were estimated to be anti-HCV positive [7] and one sixth (2.3 million persons) are living with HIV [5]. Besides, the prevalence of HCV in patients with hemodialysis is at least 5-times higher than the general population [8]. As a consequence, the perspective of HCV infection management depends not only the HCV infection itself but also the comorbidity status.

Threat of HCV Infection and Related Risk Factors

96% death due to viral hepatitis worldwide is related to chronic hepatitis B (60%) and chronic hepatitis C (30%)

[3]. Decompensated cirrhosis and hepatocellular carcinoma (HCC) are two leading causes of death in CHC [3]. High proportion up to 70-80% HCV infected individuals become chronic carriers, 15-25% of the chronic carrier eventually develop to cirrhosis within 25 years, and 25% of the patients with cirrhosis progress to HCC and/or decompensated liver disease [9,10]. Despite of the threat of HCV infection, the asymptomatic acute HCV infection and the silent progression of CHC to cirrhosis result in unawareness of infection status in half of the infected individuals. Several cofactors were demonstrated to accelerate progression towards end-stage liver disease. According to the large-scale community-based prospective study with a mean duration of 9.2 years of follow-up in Taiwan [11], the development of HCC is associated with older age, HBsAg carrier, alcoholism, cigarette smoking, abnormal liver function test, family history of cirrhosis or liver cancer. Insulin-resistance, obesity and male gender were also shown an association with rapid progression of HCV disease in other studies. In addition, a meta-analysis showed that patients with HCV/HIV infections were associated with 2.9-fold risk of progression, liver disease to cirrhosis or decompensated liver disease than patients with HCV mono-infection [12,13]. Viral genotype and host genetic factors are also playing an important role in disease prognosis and treatment response. In terms of host genetic factors, genome-wide association studies demonstrated that HCV genotype-1 infected hosts with SNP near the IL-28B gene tends to have more spontaneous HCV clearance without treatment as well as higher response rate following PegIFN/RBV treatment [14-16]. Furthermore, the IL-28B SNP also increases SVR in genotype 2/3 HCV infected patient without RVR [17]. The disparate frequency of IL28B polymorphism also accounts for higher response to IFN-based treatment in Asians or whites than in African Americans [18-20]. Therefore, management of chronic hepatitis C remains much to be considered.

The Cascade of Treating Evolution

The goal of HCV treatment is to cure of the infection and prevent disease progression. Curing HCV results in decreased all-cause mortality, liver-related death, liver transplantation and hepatocellular carcinoma [21-23]. Cure of HCV infection is achieved in more than 99% of the patients with undetectable HCV RNA 12 or 24 weeks after treatment completion, which defined as a sustained virological response (SVR) [24,25]. An achievement of SVR corresponds to cure of HCV infection with a very low chance of late relapse [25]. Interferon (IFN)-based regimens have been served as the traditional treatment of choice for HCV treatment since 1990's. The development of ribavirin (RBV) in 1991 and pegylated-interferon (PegIFN) in 2001 were a milestone in HCV treatment once upon a time. The combination therapy of PegIFN and RBV (PegIFN/RBV) remarkably elevated SVR from less than 10% with interferon monotherapy up to 50% [10]. Treatment of HCV with PegIFN/RBV lasts

more than a decade and decrease of HCV infection incidence was reported in several studies through effective therapy and public strategies. However, the SVR rate of combination of PegIFN/RBV remains unsatisfied and has heterogeneity in various patient groups. Patients with HCV genotype 2 or 3 infection has 70-80% SVR after 24 weeks of treatment duration but patients with HCV genotype 1 or 4 infection only have 40-50% SVR even after 48 weeks of treatment duration [16]. As previously mentioned, patients with SNP of the IL28B (rs12979860 CC and rs8099917 TT alleles) are demonstrated to be the independent factor of higher SVR [26]. In addition to the poor response rate in overall patient receive IFN-based therapy, considerable patients discontinued the treatment due to intolerable to adverse reactions. Treatment of chronic hepatitis C has been evolved dramatically since the introduction of oral direct antiviral agents (DAAs). The newly developed IFN-free regimens lead to considerable high SVR, short treatment duration and favorable tolerability. DAAs are molecules targeting nonstructural (NS) viral proteins of HCV, which are essential for viral replication. Current DAAs include NS3/4A protease inhibitors, NS5B RNA-dependent RNA polymerase inhibitors and NS5A inhibitors. Not DAAs are created equally and combination of two to three DAAs can attain SVR more than 90% [27]. The first generation of DAAs are boceprevir and telaprevir (released in 2011). Both of them are NS3/4A protease inhibitors and approved in combination of with PegIFN α /RBV in genotype 1 infection. These agents are soon replaced with newer DAAs due to high pill burden, drug-drug interactions, narrow genotype specificity, low barrier to resistance, addictive side effect to original PegIFN/RBV therapy, as well as costs of the treatment [10,28]. The second generation of the PIs and other DAAs not only ameliorate shortcomings of the first generation of PI but also improve SVR up to 90-100%. In addition to superior efficacy and safety profile, the new DAAs also demonstrated to have positive impacts on patient-reported outcomes (PROs), which can be a surrogate marker of patients' treatment experiences (including health related quality of life (HRQL), work productivity, physical/social function, emotion, and fatigue etc.). The PROs improved significantly early after initiation of the treatment (week 4), sustained during the treatment duration, and grow to more prominent at the end-of treatment [29-32]. It should be mentioned that early development of DAAs focused on genotype 1 because this type of infection dominates HCV infection (40~50%) around the world [5]. However, Genotype 1 accounts for most of the infections in high- and upper-middle income countries, genotype 4, 5 and 6 constitute 25% of global HCV infections and particularly clustered in resource-limited countries where most patients with HCV remains undertreated [5,33]. Therefore, the newly developed pangenotypic DAAs not only potently effective, but also shed light on curing of the infection in resource-limited settings [33] (Table 1).

Table 1: DAAs for hepatitis C [9,10,16,24,25,42,48].

DAA	Class	Approval	Genotype	Barrier to resistance	Potency	Combination (SVR)
Boceprevir	NS3/4A PI	2011	1	Medium	High	RBV + IFN (SVR 61-75%)
Telaprevir	NS3/4A PI	2011	1	Low	High	RBV + IFN (SVR 69-83%)
Simeprevir (SIM)	NS3/4A PI	2013	1, 4	Low	High	with RBV + IFN (SVR79-86%) or with SOF (SVR 95-97%)
Asunaprevir (ASV)	NS3/4A PI	2013	1b	Medium	High	with DCV (SVR 82-90%)
Paritaprevir/r (PTV/r)	NS3/4A PI (ritonavir boosted)	2013	1, 4	Low	High	with OBV + DSV ± RBV (SVR 90-99%)
Grazoprevir (GZR)	NS3/4A PI	2016	1, 4	Low	High	with EBR (SVR 92-99%)
Sofosbuvir (SOF)	NS5B	2013	Pangenotype	High	High	with RBV + IFN (SVR 89-90%) or with RBV (SVR 97% in GT2/3; SVR 68-84% in GT1) or with SIM (SVR 95-97%) or with LDV (SVR 97-99%) or with VEL (SVR 95-99%) or with DCV (SVR 95-100%)
Dasabuvir (DSV)	NS5B	2014	1	Low	Low	with OB + PTV/r ± RBV (SVR 90-99%)
Ledipasvir (LDV)	NS5A	2014	1, 4, 5	Low	High	with SOF (SVR 97-99%)
Ombitasvir (OBV)	NS5A	2014	1, 4	Medium	High	with PTV/r plus DSV ± RBV (SVR 90-99%)
Daclatasvir (DCV)	NS5A	2014	Pangenotype	Low	High	with SOF (SVR 91-100%)
Elbasvir (EBR)	NS5A	2016	Pangenotype	Medium	High	with GZR (SVR 92-99%)
Velpatasvir (VEL)	NS5A	2016	Pangenotype	Low	High	with SOF (SVR 97-99%)
Voxilaprevir (VOX)	NS3/4A PI	2017	Pangenotype	High	High	with SOF+VEL (SVR 97-99%)
Glecaprevir (GLE)	NS3/4A PI	2017	Pangenotype	High	High	With PIB (SVR 99%)
Pibrentasvir (PIB)	NS5A	2017	Pangenotype	High	High	With GLE (SVR 99%)

Current Guideline Recommendations

Generally, choices of treatment should be based on HCV genotypes, cirrhosis status, tolerability, renal/liver function, comorbidities, drug-drug interactions, patient preference, and affordability [28]. Current released guidelines suggest DAAs over Peg/IFN therapy if DAAs is affordable [16,24,25,34]. Among the DAAs, Simeprevir (SIM), Paritaprevir/r (PTV/r), Grazoprevir (GZR), Ombitasvir (OBV) are effective for the treatment of genotype 1 and 4; Ledipasvir (LDV) is effective for genotype 1, 4, and 5; sofosbuvir (SOF), Daclatasvir (DCV) and the newly developed Elbasvir (EBR), velpatasvir (VEL), voxilaprevir (VOX), Pibrentasvir (PIB), and Glecaprevir (GLE) are pangenotypic DAAs. Despite the development of the DAAs, there still leave some difficultly managed clinical situations, such as fail to DAAs treatment (< 5%), especially NS5A inhibitors; genotype 3 HCV infection with cirrhosis; decompensated cirrhosis; and in resource limited regions which are lack of access to therapy

[35]. Recently, the excellent efficacy and safety of the newly developed pangenotypic DAA treatments were demonstrated in the ASTRAL, POLARIS, ENDURANCE and SURVEYOR trials. In ASTRAL-1, -2, and -3, the overall SVR following treatment with SOF/VEL for 12 weeks was extremely high as 98% (99% SVR in genotype 1, 2, 4, 5, 6; 95% SVR in genotype 3 [36-38]; besides, the SVR was not affected in treatment-experienced patients (> 99% SVR) even in the presence of resistance-associated substations or compensated cirrhosis (99% SVR). However, if patients with decompensated cirrhosis, SOF/VOL is suggested to extend the treatment duration to 24 weeks or to combine with ribavirin for 12 weeks of treatment, which resulted in 86-94% SVR [39]. SOF/VEL/VOX, the first triple-DAA fixed dose combination, was demonstrated to have overall 95% SVR for DAA-naïve HCV genotype 1-6 patients after a shorten treatment duration as 8 weeks in POLARIS-2 [40]; besides, the SVR was even high as 99% in genotype 3 shown in the subgroup analysis. In DAA-naïve patients with HCV geno-

type 3 related compensated cirrhosis, treatment with 8-week SOF/VEL/VOX brought to 96% SVR in POLARIS-3 [40]. In POLARIS-1 and -4 [41], DAA-experienced patients with or without cirrhosis, 8-week SOF/VEL/VOX had 96-97% SVR [42]. But there is still no clear role of SOF/VEL/VOX in decompensated cirrhosis. The glecaprevir/pibrentasvir (GLE/PIB) treatment in genotype 1 had 99.1% and 99.7% SVR after 8 and 12 week-regimen, respectively; 98% and 99.5% SVR in genotype 2 after 8-week and 12-week regimen; 93% SVR and 99% SVR in genotype 4, 5, 6 after 8-week and 12-week regimen, respectively; and 95% SVR in genotype 3 HCV after 8 or 12-week regimen [24,43]. The AASLD/IDSA guideline [24] and EASL [25] recommended regimen with optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration. For treatment of genotype 1-6 HCV infection, both of AASLD/IDSA and EASL guidelines suggest pangenotypic SOF/VOL for the treatment. AASLD/IDSA also suggests the new pangenotypic GLE/PIB for treatment of genotype 1-6 HCV infection; whereas, SOF plus DSV is suggested in EASL guideline but is listed as an alternative choice in AASLD/IDSA guideline. In addition, AASLD/IDSA and

EASL guideline consistently suggest LDV/SOF and EBR / GRZ for treatment of genotype 1, 4 HCV infection. PTV/ OBV/r plus DSV (if genotype 1a or cirrhosis, plus RBV) is suggested for treatment of genotype 1,4 HCV infection in EASL guideline, but placed as an alternative in AASLD guideline. LDV/SOF is also recommended for genotype 5, 6 HCV infection. Based on the metabolic pathway of DAAs, there are still some clinical relevant drug-drug interactions should be carefully managed or monitored [44]. Beyond consideration of efficacy and safety results from clinical trials, for better patient care with DAAs therapy, checking drug-drug interactions before initiation DAA treatments is of importance. For example, the potent SOF/LDV is not recommended for coadministration with the widely used antiarrhythmic agent - amiodarone, due to the drug-drug interactions may result in serious symptomatic bradycardia [45]. Drug-drug interaction and dosing considerations of recommended DAAs in current guidelines are listed in Table 2. The convenient and comprehensive checking tool on the website of the University of Liverpool (<http://www.hep-druginteractions.org>) is recommended as a checking reference [46].

Table 2: Dosing considerations of the DAAs recommended in current guidelines [13,16,24,25].

DAAs	Dose	DDI	Liver impairment	Renal impairment
Ledipasvir/ sofosbuvir	1 tablet QD	Contraindicated in patient received amiodarone and rosuvastatin P-gp inducers ↓ SOF & LDV level Can be used with most of HIV ARV but LDV ↑TDF level, close monitor renal function or use TAF	No dosage adjustment	No dose adjustment in mild or moderate renal impairment. No recommended dose in eGFR < 30 ml/min or hemodialysis).
Sofosbuvir/ velpatasvir	1 tablet QD	VEL is metabolized by CYP3A4, CYP2C8, CYP2B6. Avoid use with efavirenz (↓VEL) VEL ↑TDF level, close monitor renal function or use TAF		
Simeprevir plus Sofosbuvir	1 tablet QD	Metabolized by 3A4 Should be avoided with efavirenz, nevirapine, cobicistat, or boosted protease inhibitors	Contraindicated in Child-Pugh B/C	
Daclatasvir plus Sofosbuvir	1 tablet QD	Avoid use with strong CYP3A4-inducers or -inhibitors	No dosage adjustment	
Elbasvir/ grazoprevir	1 tablet QD	Metabolized by CYP3A4 and substance of P-gp Avoid use with CYP3A4 and P-gp inducers/inhibitors (HIV protease inhibitors, NNRTI with efavirenz, Nevirapine)	Contraindicated in Child-Pugh B/C	No dosage adjustment
Glecaprevir/ pibrentasvir	1 tablet QD	Inhibitor of P-gp, BCRP, OATP. Weak inhibitor of CYP3A4, 1A2 and UGT1A1. Avoid use with HIV protease inhibitors, NNRTI with efavirenz, Nevirapine	Not recommended in Child-Pugh B and contraindicated in Child-Pugh C	No dosage adjustment

Ombitasvir/ paritaprevir/r/ plus dasabuvir	2 tablets QD plus 1 tablet BID	Metabolized by 3A4/2C8 and also 3A4/2C8 inhibitor Should be avoided with efavirenz, nevirapine, ritonavir-boosted lopinavir, ritonavir-boosted tipranavir, cobicistat, rilpivirine, darunavir	Contraindicated in Child- Pugh B/C	No dosage adjustment
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Table 3: DAAs choices in special conditions [9,16,24,25].

Condition of the patients	Suggested regimens
HBV/HCV coinfection	Risk of HBV reactivation during HCV treatment; Treatment for HBV is indicated for HBsAg (+) patients
HIV/HCV coinfection	Same recommended regimen as patients without HIV; Drug-drug interactions should be carefully evaluated.
CKD, stage 4 or 5	Elbasvir/grazoprevir (genotype 1,4), glecaprevir/pibrentasvir (genotype 1-6), or Ombitasvir/paritaprevir/r + dasabuvir (genotype 1,4)
Decompensated Cirrhosis	Genotype 1,4,5,6: Ledipasvir/sofosbuvir + ribavirin (low dose from 600 mg till tolerated) for 12 weeks Velpatasvir/sofosbuvir + weight-based ribavirin for 12 weeks (if ribavirin is not eligible, prolonged treatment course to 24 weeks) Genotype 1,4: Daclatasvir + sofosbuvir + ribavirin (low dose from 600 mg till tolerated) for 12 weeks (if ribavirin is not eligible, prolonged treatment course to 24 weeks)

Considerations for Special Populations

Some special populations have been difficultly treated with traditional PegIFN/RBV therapy with poor SVR or intolerability, such as HCV/HIV coinfection, severe renal impairment, and decompensated liver disease [27]. Patients with hemodialysis and decompensated liver disease usually halter IFN or RBV treatment due to contraindicated labeled for their use. Managements with DAAs in these situations are described in Table 3, including patients with HBV/HCV coinfection, HIV/HCV coinfection, severe hepatic/renal impairment. For HBV/HCV coinfecting patients, HCV often dominates the chronic inflammation and HBV viral load is usually low or undetectable. Thus, there is potential risk of HBV reactivation following treatment for HCV [25]. Although the clinical impact of the increased HBV viral load is unpredictable, concurrent HBV treatment is indicated for this population. Treatment suggestions for HIV/HCV infection are the same as those for patients with either HIV or HCV mono-infection [13]. Compared to lower cure rate with Peg/IFN treatment, DAAs are demonstrated to have similar SVR in HIV/HCV coinfecting populations compared with HCV mono-infected patients. However, special concerns for drug-drug interactions between DAAs and antiretroviral agents (ARV) for HIV should be carefully evaluated. Most of the DAAs are undergoing hepatic metabolism but sofosbuvir (SOF) has 80% renal excretion; therefore, patients with severe renal impairment (including patients with hemodialysis) is not recommended for SOF-based regimens due to accumulation of metabolites are seen. Traditional PegIFN/RBV treatment showed lower SVR and with increased side effects in patients with cirrhosis than those without

cirrhosis [9,47]; as a result, IFN-free regimens are more preferable for patients with severe liver impairment, but protease inhibitors are contraindicated for this patient group.

Conclusions

The evolution of chronic hepatitis C treatment has been evolved dramatically and change the landscape of HCV treatment. The SVR and tolerability of traditional standard PegIFN/RBV treatment remains poor, although there are some patient groups might still benefit from relatively high SVR e.g., host with IL28B polymorphisms, and infected HCV with genotype 2 or 3. The coming new era of new DAAs lead HCV treatment becomes high curability and high tolerability. Besides, the development of DAAs also revolved rapidly from narrow genotype to pangenotype, increase SVR up to > 99%, and provide better treatment options whether in high, middle and low income countries. The high SVR not only relies in Patients with HCV mono-infection but also comparable in patients with HCV/HIV coinfection, whose cure of HCV was usually thought to be intractable in IFN era. Although the chronic hepatitis C becomes generally curative, there are still some perspectives for clinical health caregivers for consideration based on the comorbidities.

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Statement of Equal Authors' Contribution

The authors have equal contribution on paper review and manuscript.

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