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MINIREVIEWS

Update on hepatitis C: Direct-acting antivirals

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Abstract

Hepatitis C virus (HCV) was discovered 26 years ago. For decades, interferon-based therapy has been the mainstay of treatment for HCV. Recently, several direct-acting antivirals (DAAs) have been approved for treatment of HCV-infected patients and to help combat the virus. These drugs have revolutionized the management of HCV as all-oral regimens with favorable side effect profiles and superior rates of sustained virological response. Emerging real-world data are demonstrating results comparable to registration trials for DAA agents. Suddenly, the potential for eradicating HCV is on the horizon.

Key words: Hepatitis C virus; Direct-acting antivirals; Sustained virologic response; Management; Treatment

Core tip: Recently, several direct-acting antivirals (DAAs) have been approved for treatment of hepatitis C virus (HCV)-infected patients and to help combat the virus. These drugs have revolutionized the management of HCV as all-oral regimens with favorable side effect profiles and superior rates of sustained virological response. Emerging real-world data are demonstrating results comparable to registration trials for DAA agents. Suddenly, the potential for eradicating HCV is on the horizon.

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INTRODUCTION

Hepatitis C virus (HCV) was discovered 26 years ago in 1989, previously the HCV-related clinical entity was referred to as non-A, non-B hepatitis[1]. Currently, HCV has created a major health burden, with approximately 180 million infected people worldwide, representing about 2%-3% of the world's population[2]. This single-stranded, positive-sense 9.6 kb RNA-virus is globally

prevalent, showing geographic variation in its genotypic distribution and represents a major cause of end-stage liver disease[3,4]. About 4 out of 5 patients acutely infected with HCV develop a chronic hepatitis while only 20% of patients demonstrate spontaneous recovery with eradication of HCV[5]. Chronic hepatitis C (CHC) is a leading cause of cirrhosis and is complicated by development of hepatocellular carcinoma in 1%-4% of cirrhotic patients[6,7].

Until recently, interferon (IFN)-based therapies represented the mainstay of treatment for HCV infection. Modifications of the treatment-regimens including pegylation of IFN and the addition of ribavirin (RBV) resulted in suboptimal improvement sustained virologic response (SVR) and an unfavourable adverse effects profile. Based on the HCV genotype (GT) and the treatment-experience, only 40% to 70% of patients achieved SVR, with poorer outcomes among people infected with the more prevalent GT1[8]. The approval of the first-generation direct acting antiviral (DAA) agents, telaprevir (TLV) and boceprevir (BCV), in 2011 provided improvement in SVR for the targeted HCV GT1[9]. Unfortunately, TLV and BCV therapy was complicated by cumbersome schema of drug intake and the broad range of adverse events.

With the release of sofosbuvir in 2013 and 2014 in most Western countries, a new era in the treatment of CHC began. An all-oral, IFN-free antiviral treatment for CHC with DAA agents became available for the first time. In addition to sofosbuvir, approvals of other second-generation DAA agents, which target different proteins of HCV have improved the efficacy of antiviral therapy with better tolerance. The superior SVR rates from several phase Ⅲ trials have recently been confirmed by a number of real-life experience reports. We review various DAA-based antiviral regimens for HCV-infected patients.

MOLECULAR STRUCTURE OF HCV - TARGET SITES FOR DAA AGENTS

HCV is a member of the Flaviviridae virus family[10-12]. Its RNA is single-stranded and positive-sensed with a size of approximately 9.6 kb. The precursor-polyprotein is post-translationally processed and modified by a cooperation of cellular and viral proteases[13,14]. Bench molecular biology research on HCV has led to a better understanding of its replication cycle and has been instrumental in the discovery and development of molecules blocking viral proteins, specifically the DAAs[15-17]. The HCV-genome encodes for 9 proteins - 2 are structural (E1 and E2) and 7 non-structural (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B)[10,11,13,14]. These proteins provide targets for the DAAs, being mostly essential in the virus cycle of replication[10-14]. NS5B is a polymerase and a prime target for antiviral agents[18,19]. Antiviral agents are classified as inhibitors of nucleoside-type and non-nucleoside type. The active site of NS5B is highly conserved compared to other parts of the HCV-genome[18,19]. Currently, sofosbuvir is the only clinically available NS5B-inhibitor (nucleoside-type) with pan-genotypic antiviral activity and higher barrier to resistance compared to other DAAs[18,19]. It is a pro-drug and currently represents the backbone of most treatment-regimens[20,21]. Inhibition of the NS3/4A protease-complex is another potential target for DAAs. The first-generation DAAs, TLV and BCV were inhibitors of NS3/4A, and referred to as protease-inhibitors. Currently, two NS3/4A-inhibitors are approved in the United States and the European Union - paritaprevir, which is approved for the treatment of HCV GT1 in combination with ombitasvir and dasabuvir; and simeprevir, which is approved in combination with sofosbuvir for GT1 patients. DAAs targeting NS5A have also been approved[22-25]. Currently, three different NS5A-Inhibitors are approved in the United States and/or the European Union - daclatasvir, which is given in combination with sofosbuvir ± RBV for the treatment of the GTs 1-4; ombitasvir (ABT-267), which is approved for the treatment of GT1 in combination with paritaprevir and dasabuvir; and ledipasvir, which is approved for GT1, 3 and 4 in combination with sofosbuvir ± RBV.

DAA AGENTS - REGIMEN BASED ON HCV GT

With the approval of sofosbuvir in December of 2013 in North America (United States and Canada) and in January 2014 in Europe, an all-oral antiviral treatment for CHC with DAAs was available for the first time. In 2014, several studies analyzing the efficacy and the impact of the DAA-based therapies have been published. The response rates have been reproduced in real-life experiences (TRIO and TARGET 2.0) as well[26-29].

HCV GT1 is the most common GT with an overall prevalence of 46.2%. In particular, GT1 is more prevalent in the Western countries of North America and Western Europe (75.8% and 59.0% respectively). Accordingly, most studies have focused on the treatment of GT1. Patients with GT2 and GT3 are less prevalent worldwide (GT2 9.1% and GT3 30.1%) with a noticeable variation in distribution within Western countries - North America (GT2 12.0% and GT3 10.4%) and Western Europe (GT2 10.8% and GT3 24.8%). Patient with GT 4, 5 and 6 demonstrate the lowest prevalence (GT4 8.3%, GT5 0.8%, and GT6 5.4%) worldwide, with highest prevalence in low-income countries, and limited data on experience with second-generation DAA agents[4].

In phase-3 SAPPHIRE-Ⅰ clinical trial the combination of ritonavir-boosted ABT-450/r (protease inhibitor)-ombitasvir (NS5A inhibitor), and dasabuvir (non-nucleoside NS5B) with RBV were studied in treatment-naïve, non-cirrhotic HCV-infected non-cirrhotic patients with GT1. RBV was added according to body weight (≥ 75 kg 1200 mg/d or < 75 kg 1000 mg/d). Overall, 96.2% of patients achieved SVR (GT1b 98.0% and GT1a 95.3%). A higher stage of fibrosis and obesity were the negative predictive factors with SVR-12 rates still > 90% and thus satisfactory[30]. Treatment-experienced patients were studied in the SAPPHIRE-Ⅱ clinical trial.

Table 1 Direct-acting antiviral-based regimens for treatment-naïve hepatitis C virus-infected patients

Genotype	Recommended regimens options
GT1a	SOF/LDV × 12 wk
	PrOD + RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis)
	SOF + SMV ± RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis without Q80K variant)
	SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV)
GT1b	SOF/LDV × 12 wk
	PrOD + RBV × 12 wk
	SOF + SMV ± RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis)
	SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV)
GT2	SOF + RBV × 12 wk (no cirrhosis) - 16 wk (cirrhosis)
	SOF + DCV × 12 wk (RBV intolerant)
GT3	SOF + PegIFN + RBV × 12 wk (PegIFN eligible)
	SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV)
	SOF + RBV × 24 wk (PegIFN ineligible)
GT4	SOF/LDV × 12 wk
	PrO + RBV × 12 wk
	SOF + RBV × 24 wk
	SOF + PegIFN + RBV × 12 wk
	SOF + SMV ± RBV × 12 wk
GT5	SOF/LDV × 12 wk
	SOF + PegIFN + RBV × 12 wk
GT6	SOF/LDV × 12 wk
	SOF + PegIFN + RBV × 12 wk

GT: Genotype; SOF: Sofosbuvir; LDV: Ledipasvir; PrOD: Paritaprevir + ritonavir + ombitasvir + dasabuvir; RBV: Ribavirin; SMV: Simeprevir; DCV: Daclatasvir; PegIFN: Pegylated interferon.

Table 2 Direct-acting antiviral-based regimens for treatment-experienced hepatitis C virus-infected patients

Genotype	Recommended regimens options
GT1a	SOF/LDV[1] × 12 wk (no cirrhosis) - 24 wk (cirrhosis[2])
	PrOD + RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis)
	SOF + SMV ± RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis without Q80K variant)
	SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV)
GT1b	SOF/LDV[1] × 12 wk (no cirrhosis) - 24 wk (cirrhosis)
	PrOD + RBV × 12 wk
	SOF + SMV ± RBV × 12 wk (no cirrhosis) - 24 wk (cirrhosis)
	SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis and ± RBV)
GT2	SOF + RBV × 16-24 wk
	SOF + PegIFN + RBV × 12 wk
GT3	SOF + PegIFN + RBV × 12 wk (PegIFN eligible)
	SOF + DCV × 12 wk (no cirrhosis) - 24 wk (cirrhosis ± RBV)
GT4	SOF/LDV × 12 wk
	PrO + RBV × 12 wk
	SOF + RBV × 24 wk
	SOF + PegIFN + RBV × 12 wk
	SOF + SMV ± RBV × 12 wk
GT5	SOF/LDV × 12 wk
	SOF + PegIFN + RBV × 12 wk
GT6	SOF/LDV × 12 wk
	SOF + PegIFN + RBV × 12 wk

[1]Add RBV if previously treated with SOF + RBV or SOF + PegIFN + RBV; [2]Alternative option SOF/LDV + RBV × 12 wk. GT: Genotype; SOF: Sofosbuvir; LDV: Ledipasvir; PrOD: Paritaprevir + ritonavir + ombitasvir + dasabuvir; RBV: Ribavirin; SMV: Simeprevir; DCV: Daclatasvir; PegIFN: Pegylated interferon.

Again, a high grade of fibrosis and obesity were negative predictive factors, with an overall SVR-12 of 96.3% (GT1a 96% and GT1b 96.7%)[31].

The ION clinical trials (ION-Ⅰ, ION-Ⅱ and ION-Ⅲ) examined the efficacy of sofosbuvir and ledipasvir co-formulation with and without RBV for 12 to 24 wk in treatment-naïve (16% with cirrhosis) HCV-infected GT1 patients[31]. SVR-12 was 97%-99% in ION-Ⅰ clinical trial. There was no statistically significant difference between the duration of the treatment (12 wk *vs* 24 wk), HCV sub-GT (GT1a *vs* GT1b) or RBV use. Even the presence of cirrhosis did not impact the SVR[32,33]. Treatment-experienced HCV-infected GT1. Patients were treated with sofosbuvir and ledipasvir co-formulation ± RBV for 12 or 24 wk in ION-Ⅱ clinical trial. In these patients, addition of RBV did not impact the SVR. Previously treated patients with cirrhosis were the only sub-group that demonstrated a higher SVR with 24 wk of therapy. Therefore, 24 wk of treatment was recommended for previously treated patients with cirrhosis[34]. In The ION-Ⅲ clinical trial, the possibility of shortening the treatment to 8 wk in previously untreated patients without cirrhosis was evaluated. A high number of patients reached SVR in all groups (93% to 95%) without a significant impact of the duration of the treatment or the addition of RBV in the 8-wk treatment[35]. Based on secondary analysis, patients with baseline HCV RNA level greater than 6 million international units per milliliter demonstrated a higher risk of relapse with 8 wk of therapy. Therefore, 8 wk of therapy is recommended for treatment-naïve, non-cirrhotic HCV-infected patients with pre-treatment HCV RNA viral load of less than 6 million international units per milliliter[35].

In the COSMOS trial, the SVR to sofosbuvir and simeprevir combination in previous non-responders with METAVIR scores between F0 and F2 was compared to previous non-responders and treatment-naive patients with METAVIR scores between F3 and F4. The SVR-12 rates were similar in both groups, showing 90% SVR-12 in patients with METAVIR scores F0-F2 and 94% SVR-12 in patients with METAVIR score F3-F4. Neither the duration of the treatment (12 wk *vs* 24 wk) nor the addition of RBV seemed to influence the SVR[36].

The combination of sofosbuvir and daclatasvir DCV has been safe and effective, both, in previously treated and untreated HCV-patients with GT1[37,38]. In previously untreated HCV-infected GT1 patients, a SVR-12 of 98% was achieved with no significant impact of the duration of the treatment (12 wk *vs* 24 wk) or the addition of RBV[37]. In previously treated patients, 24 wk of treatment with sofosbuvir and daclatasvir demonstrated a SVR-12 of 97.5% with no influence from RBV addition[37].

Please refer to Tables 1 (treatment-naïve) and 2 (treatment-experienced) for treatment recommendation by HCV GT with DAA agents[38-44].

CONCLUSION

The current developments in the treatment of CHC are extraordinary. A significant improvement in efficacy

provided by the DAA agents has been long awaited. In addition to higher efficacy, DAA agents are tolerable with favorable adverse effects profile. Improved efficacy combined with easy tolerability is welcome news for a wide spectrum of patients who were not able to pursue interferon-based antiviral therapy for CHC. Impediments to DAA-based therapy include the high cost of therapy. Efforts are underway to make DAA agents affordable in Asia and Africa. Other issues include a cumbersome insurance authorization process in the United States. Importance of screening patients with risk factors for CHC and linkage to care remains a global issue. It is important to educate the patients that HCV treatment with DAA agents does not confer immunity and exposure to risk factors can lead to re-infection.

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