Review Article

Direct-acting Antiviral Agents for the Treatment of Chronic Hepatitis C Virus Infection

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Abstract

Hepatitis C virus (HCV) is a leading cause of cirrhosis and hepatocellular carcinoma (HCC) in the US and Japan. Therefore, eradication of HCV may reduce the occurrence of HCC in HCV-infected individuals. In 2011, the use of first-generation HCV NS3/4A protease inhibitors such as telaprevir and boceprevir was initiated for clinical treatment of HCV. Administration of telaprevir and boceprevir plus peginterferon and ribavirin increased rates of sustained virological response (SVR) in HCV genotype 1-infected patients. However, this treatment regimen also led to severe adverse events. Second-generation direct-acting antiviral agents (DAAs) for HCV, such as simeprevir plus peg-interferon and ribavirin also resulted in higher SVR rates, with similar adverse events to other peg-interferon and ribavirin treatments. Higher SVR rates in HCV genotype 1- and 2-infected patients were achieved with 12-16 weeks of sofosbuvir plus other class DAAs with/without ribavirin and 12 weeks of sofosbuvir plus ribavirin, respectively. For "difficult-to-treat" HCV-infected patients, more therapeutic options are needed. Further studies examining the efficacy and adverse effects of such therapies will be required for the development of additional treatments.

Introduction

Hepatitis C virus (HCV) causes acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).[1,2] Eradication of HCV by (peg-)interferon with or without ribavirin prevents chronic HCV patients from progressing to hepatic fibrosis, HCC, and hepatic failure, and improves survival rates.[3–7] Even in HCV-infected patients with histologically proven cirrhosis, achievement of sustained virological response (SVR) after treatment was associated with a reduction of liver-related mortality and HCC development,[8] although the risk of occurrence was not completely eliminated.[8,9]

HCV is an enveloped positive-stranded RNA virus belonging to the genus *Hepacivirus*, a member of the *Flaviviridae* family. The HCV genome is ~9,600 nt in length and contains a 5′ nontranslated region (5′NTR), a single open reading flame, and a 3′NTR. A single polyprotein translated from the HCV genome is processed by HCV proteases, including HCV NS2 cysteine protease, HCV NS3 serine protease, and host proteases, into structural (core, E1, E2 and p7) and non-structural (NS2, NS3, NS4A, NS4B, NS5A and NS5B) proteins.[10] The HCV RNA replication complex forms in the endoplasmic reticulum, and a phosphoprotein HCV NS5A and an RNA-dependent RNA polymerase HCV NS5B, make a positive-stranded RNA from negative-stranded RNA as a template. Subsequently, HCV virions are produced and egress from hepatocytes into human blood. Direct-acting antiviral agents (DAAs) against HCV specifically target one of these proteins and strongly inhibit HCV replication, and interferon and/or ribavirin could non-specifically inhibit HCV replication in addition to other viral replications. Fig. 1 shows HCV-coding proteins and their representative DAAs.[10]

Peg-interferon with ribavirin has been the standard of care (SOC) treatment for HCV-infected individuals.[10] Although this treatment led to ~80% SVR in patients infected with HCV genotype 2 or 3, it only led to ~50% SVR in patients infected with HCV genotype 1 and those with high viral loads.[10,11] In 2011, protease inhibitors such as boceprevir and telaprevir were available for HCV genotype 1-infected individuals in US, Japan, and other countries. Although protease inhibitor-including regimens for patients infected with HCV genotype 1 always received simultaneous peg-interferon with ribavirin treatments, these regimens have achieved 70~80% SVR in treatment-naïve patients or previously treated relapsers.[12–18] Protease inhibitor-including regimens are now considered the SOC treatment for HCV genotype 1-infected patients, although peg-interferon with ribavirin treatment is considered the SOC for HCV genotype 2 or 3 infection. However, interferon therapy is beset by well-known adverse events, including influenza-like symptoms, cytopenia, and depression, and the lack of response in some patients to interferon therapy has been disappointing. These adverse events prevent "difficult-to-treat" patients from eradicating this virus.[19] In the near future, the use of interferon-free treatment strategies will likely play a central role in the treatment of chronic HCV infection. In this review article, we focus on protease inhibitor containing regimens and interferon-free regimens against chronic HCV infection.

Keywords: Daclatasvir; Interferon-free; Protease inhibitors; Simeprevir; Sofosbuvir.
Abbreviations: DAA, direct-acting antiviral agent; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NS, non-structural protein; SNP, single nucleotide polymorphism; SOC, standard of care; SVR, sustained virological response.
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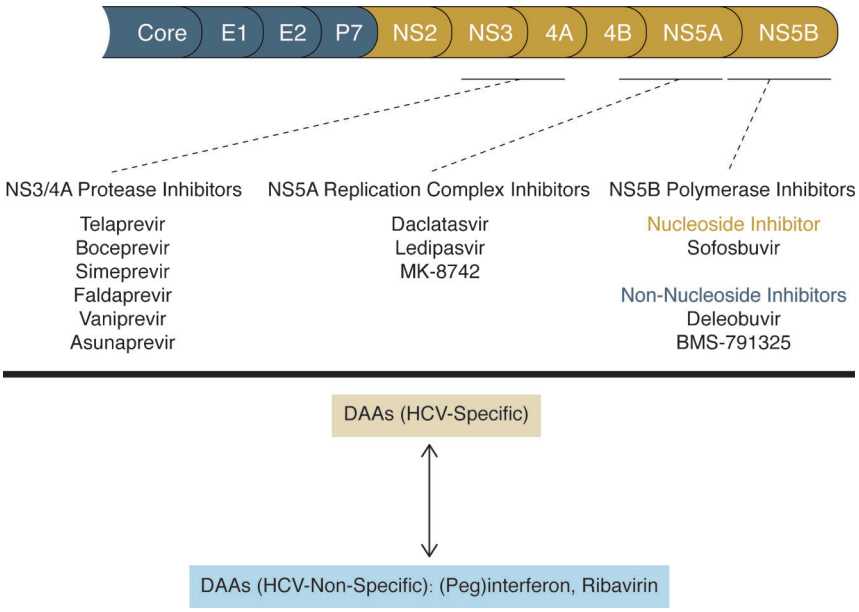

Fig. 1. HCV-coding proteins and their representative direct-acting antiviral agents (DAAs). Structural and non-structural (NS) proteins are core, E1, E2, and p7, and NS2, NS3, NS4A (4A), NS4B (4B), NS5A, and NS5B, respectively.[10]

First-generation protease inhibitors: telaprevir and boceprevir

Telaprevir and boceprevir are two of the first generation oral HCV NS3/4A protease inhibitors.[16] SVR rates in telaprevir-based triple therapy in HCV genotype 1-infected treatment-naïve and treatment-experienced patients were 69–75% and 51–52%, respectively.[12,20] SVR rates in boceprevir-based triple therapy in HCV genotype 1-infected treatment-naïve and treatment-experienced patients were 63–66% and 59–66%, respectively.[15,16] Telaprevir and boceprevir must be used in combination with peg-interferon with ribavirin for optimal efficacy, and although occasionally this combination is associated with serious adverse events, it markedly improved SVR rates in HCV genotype 1-infected patients.[17,21–23] D'Ambrosio and Colombo reported that the rates of treatment discontinuation due to adverse events were as high as 14%.[24] Since it is possible that telaprevir and boceprevir induce drug-resistance mutations, peg-interferon with ribavirin or their combination with other class DAAs is absolutely necessary with their use.

Second-generation protease inhibitors: simeprevir, faldaprevir, and vaniprevir

Simeprevir (TMC435) is an oral, once-daily (QD), HCV NS3/4A macrocyclic protease inhibitor with potent antiviral activity in HCV genotype 1-infected patients as well as HCV genotypes 2, 4, 5 and 6.[25] Protease Inhibitor TMC435 trial assessing the optimal dose and duration as once daily anti-viral regimen (PILLAR) is an ongoing study in 13 countries in North America, Europe and Asia-Pacific regions, and showed that simeprevir administered QD with peg-interferon-alpha-2a and ribavirin in treatment-naïve patients infected with HCV genotype 1 for 24–48 weeks resulted in 75–86% SVR (versus 65% in placebo with peg-interferon-alpha-2a and ribavirin-treated group).[25] Simeprevir QD in combination with peg-interferon and ribavirin significantly improved SVR rates, and the majority of patients shortened their treatment duration to 24 weeks. Of importance, the adverse event profile of simeprevir was generally similar to that of control, with the exception of mild reversible hyperbilirubinemia, without serum aminotransferase abnormality.[25] A Japanese study also showed that simeprevir administered QD with peg-interferon-alpha-2a and ribavirin in treatment-naïve patients infected with HCV genotype 1, aged 20–70 years, for 24 weeks resulted in 77–92% SVR (versus 46% in placebo with peg-interferon-alpha-2a and ribavirin-treated group).[26] Unlike telaprevir or boceprevir, simeprevir appeared generally safe and well tolerated.[25,26] V36A/M/L/G, T54A/S, V55A, Q80K/R/H/G, R155K/T/I/M/G/L/S/Q, A156V/T/S/I/G, D168A/V/E/G/N/T/Y/H/I, and V170A have been identified as amino acid substitutions resistant to NS3/4A protease inhibitors, including linear ketoamides (telaprevir, boceprevir, and faldaprevir) and macrocyclic compounds (vaniprevir and simeprevir).[27–29] Among simeprevir-treated patients, resistance mutations such as R155K or D168V alone or a combination of Q80K/R, R155K, and/or D168E mutations have emerged.[30] R155K and D168V were observed primarily in HCV subgenotypes 1a and 1b isolates, respectively.[30]

Faldaprevir (BI 201335) is a HCV NS3/4A protease inhibitor with pharmacokinetic properties supportive of QD dosing, with potent antiviral activity in HCV genotype 1-infected patients as well as HCV genotypes 4, 5, and 6.[31] Faldaprevir 240 mg, dosed QD in combination with peg-interferon and ribavirin, increased SVR rates of treatment-naïve HCV genotype 1 patients from 56% in the placebo group to as high as 84%.[31] Faldaprevir selected NS3 mutants predominantly encoded for R155K and D168V in HCV subgenotypes 1a and 1b, respectively.[31] Faldaprevir 240 mg QD, in combination with peg-interferon and ribavirin, led to SVR in ~35% or 50% of HCV genotype 1 patients with strictly defined prior null or partial response to peg-interferon and

ribavirin treatment, respectively.[32] A preliminary Japanese study also showed that faldaprevir with peg-interferon and ribavirin was efficacious and well tolerated.[33]

Vaniprevir, a HCV NS3/4A protease inhibitor, with peg-interferon and ribavirin, significantly increased SVR rates among treatment-experienced patients with chronic HCV genotype 1 infection, compared to retreatment with peg-interferon and ribavirin alone.[34]

Interferon-including regimens

The presently approved HCV NS3/4A protease inhibitors such as telaprevir- and boceprevir-containing regimens must be combined with peg-interferon and ribavirin for their use against HCV genotype 1 to prevent generation of resistant mutants during the treatment.[12–16,20] Without combining with other DAAs, second-generation HCV NS3/4A protease inhibitors should be used together with peg-interferon plus ribavirin for HCV genotype 1-infected patients.[35] Genome-wide association studies showed a potent association between single nucleotide polymorphisms (SNPs) near the IL28B gene and the treatment response of peg-interferon plus ribavirin therapy.[36–38] Although the IL28B SNPs still have an impact on the treatment response against 24-week telaprevir-based triple combination therapy for patients with HCV genotype 1,[39] boceprevir and telaprevir attenuated the association between IL28B SNPs and treatment response.[40] Due to the adverse events of peg-interferon plus ribavirin, patients with contra-indications to peg-interferon plus ribavirin treatment are also not candidates for boceprevir- or telaprevir-based triple therapy.[19] The benefits of the addition of one DAA to peg-interferon plus ribavirin treatment would be limited by the underlying issues of safety and tolerability.[41]

Interferon-free regimens

The oral combination of different DAAs holds promise as an interferon-free treatment for chronic HCV infection.[41] In the near future, the use of all-oral DAAs and interferon-free regimens for the treatment of HCV-infected patients with a potent antiviral effect against HCV and with less adverse events may be a viable therapeutic option.[18] Of course, IL28B SNPs do not have an impact on the treatment response of interferon-free regimens, and interferon-free regimens seem to improve the SVR rates in HCV genotype 1-infected patients with IL28B minor genotypes.

Sofosbuvir

Sofosbuvir (GS-7977; formerly PSI-7977) is a pyrimidine nucleoside analog inhibitor of HCV pangenotype NS5B polymerase.[42] The addition of sofosbuvir to peg-interferon plus ribavirin treatment could lead to an SVR of 90–91% and 92% in HCV genotype 1 patients treated for 24–48 weeks, and HCV genotype 2 patients treated for 12 weeks, respectively.[43] In HCV genotype 1-infected patients receiving sofosbuvir 400 mg plus peg-interferon and ribavirin for 12 weeks, for 24 weeks, or 12 weeks of sofosbuvir plus peg-interferon and ribavirin followed by 12 weeks of either sofosbuvir monotherapy or sofosbuvir plus ribavirin, SVRs of 89%, 89%, or 87% were achieved, respectively.[44] In HCV genotype 4- and 6-infected patients who received sofosbuvir 400 mg plus peg-interferon and ribavirin for 24 weeks achieved SVRs of 82% and 100% were achieved, respectively.[44] These results suggest that simple and short sofosbuvir-based regimens may be effective for HCV-infected individuals.[43,44]

Among HCV genotype 2- or 3-infected patients for whom treatment with peg-interferon was not an option, the SVR rate was 78% with 12 weeks of sofosbuvir and ribavirin, as compared to 0% with placebo.[45] Among previously treated patients, the SVR rate was 50% with sofosbuvir and ribavirin for 12 weeks and 73% for 16 weeks. SVR rates were lower among HCV genotype 3-infected patients than among those with HCV genotype 2.[45] Twenty-four weeks of treatment with sofosbuvir and ribavirin for HCV genotype 1-infected patients with unfavorable treatment characteristics resulted in 40–68% SVR rates.[46] Twelve weeks of sofosbuvir and ribavirin treatment seemed excellent for HCV genotype 2 infection, but even 24 weeks of sofosbuvir and ribavirin treatment was insufficient against HCV genotype 1 infection.

An interferon-free regimen-at-fixed-dose combination of sofosbuvir (400 mg) and the HCV NS5A inhibitor ledipasvir (90 mg), with and without ribavirin, led to 95–100% SVR rates in patients with HCV genotype 1 infection who were treatment-naïve or previously treated with protease-inhibitor regimen, irrespective of treatment history or the presence of compensated cirrhosis.[47] The results of sofosbuvir-based treatments are shown in Table 1. In HCV genotype 1 infection, SVR results of a once-daily regimen of simeprevir (TMC435) plus sofosbuvir (GS-7977) with or without ribavirin were 79–96% and 96–100%, in staging fibrosis of the liver of F0–F2 and F3–F4, respectively.[48] In an *in vitro* study, NS5B, S282T, and M289L were identified as resistance-associated mutations.[49]

Daclatasvir

Daclatasvir, an NS5A inhibitor identified by chemical genetics strategy, has been shown to have a potent clinical effect.[50] Dual therapy with daclatasvir and asunaprevir, NS3 protease inhibitor, led to SVR in certain HCV genotype 1-infected patients who had not a responded previously to therapy. A high rate of SVR was achieved when these two DAAs were combined with peg-interferon and ribavirin.[51,52] Results of daclatasvir-based treatments are shown in Table 2. It has been reported that there is a potent association between a pre-existing NS5A-Y93H mutation and virological failure on daclatasvir/asunaprevir combination treatment.[53] Suzuki *et al.*[54] reported that the NS5A-Y93H variant pre-existed in 23% of HCV genotype 1b-infected patients treated with dual oral therapy of daclatasvir and asunaprevir; where 50% experienced virological failure, and 50% achieved SVR. Future studies are necessary to further elucidate the clinical efficacy of daclatasvir for HCV.

Conclusions

To prevent the occurrence of HCC in chronic hepatitis C patients, it follows that HCV needs to be eradicated from these patients. For ''difficult-to-treat'' HCV-infected patients, more therapeutic options are needed. To date, sofosbuvir containing interferon-free regimens may be more efficacious, safer, and better tolerated with less adverse events than peg-interferon-based triple therapy with telaprevir and boceprevir. Further studies are needed to more fully understand efficacy and safety of new drugs, including assessment of clinical drug-drug interactions.

Table 1. Sustained virological response (SVR) rates in hepatitis C patients treated with sofosbuvir-including regimens

References	G	Number of patients	Naive	Therapy formula	SVR (%)
Lawitz *et al.* [43]	1	48	Yes	12 wk of sofosbuvir (200 mg)/peginterferon/ribavirin and 12/36 wk of peginterferon/ribavirin	85
	1	47	Yes	12 wk of sofosbuvir (400 mg)/peginterferon/ribavirin and 12/36 wk of peginterferon/ribavirin	89
	1	26	Yes	12 wk of placebo/peginterferon/ribavirin and 12/36 wk of peginterferon/ribavirin	58
	2/3	25	Yes	12 wk of sofosbuvir (400 mg)/peginterferon/ribavirin and 12/36 wk of peginterferon/ribavirin	92
Kowdley *et al.* [44]	1	52	Yes	12 wk of sofosbuvir (400 mg)/peginterferon/ribavirin	89 (ITT)
	1/4/6	125	Yes	24 wk of sofosbuvir (400 mg)/peginterferon/ribavirin	89 (ITT)
	1	155	Yes	12 wk of sofosbuvir (400 mg)/peginterferon/ribavirin and 12 wk of either sofosbuvir monotherapy or sofosbuvir plus ribavirin	87 (ITT)
Jacobson *et al.* [45]	2/3	207	Almost	12 wk of sofosbuvir/ribavirin	78 (SVR12)
	2/3	71	Almost	Placebo	0 (SVR12)
	1/2/3	103	No	12 wk of sofosbuvir/ribavirin	50 (SVR12)
	1/2/3	98	No	16 wk of sofosbuvir/ribavirin	73 (SVR12)
Lawitz *et al.* [42]	1/4/5/6	327	Yes	12 wk of sofosbuvir/peginterferon/ribavirin	90 (SVR12)
	1/2/3	256	Yes	12 wk of sofosbuvir/ribavirin	67 (SVR12)
	2/3	243	Yes	24 wk of peginterferon/ribavirin	67 (SVR12)
Osinusi *et al.* [46]	1	10	Yes	24 wk of sofosbuvir/weight-based ribavirin	90
	1	25	Yes	24 wk of sofosbuvir/weight-based ribavirin	68
	1	25	Yes	24 wk of sofosbuvir/low-dose ribavirin	48
Lawitz *et al.* [47]	1	20	Yes	8 wk of sofosbuvir/ledipasvir	95 (SVR12)
	1	21	Yes	8 wk of sofosbuvir/ledipasvir/ribavirin	100 (SVR12)
	1	19	Yes	12 wk of sofosbuvir/ledipasvir/ribavirin	95 (SVR12)
	1	19	No	12 wk of sofosbuvir/ledipasvir	95 (SVR12)
	1	21	No	12 wk of sofosbuvir/ledipasvir/ribavirin	100 (SVR12)

G, genotype; Naïve, treatment-naïve; SVR, sustained virological response; wk, weeks

Table 2. Sustained virological response (SVR) rates in hepatitis C patients treated with daclatasvir-including regimens

References	G	Number of patients	Naive	Therapy formula	SVR (%)
Chayama *et al.* [51]	1b	10	No (Null)	24 wk of daclatasvir (60 mg)/asunaprevir (600 mg)	90 (SVR12)
Lok *et al.* [52]	1a/1b	11	No (Null)	24 wk of daclatasvir (60 mg)/asunaprevir (600 mg)	36 (SVR12)
	1a/1b	10	No (Null)	24 wk of daclatasvir (60 mg)/asunaprevir (600 mg)/ peginterferon/ribavirin	100 (SVR12)

G, genotype; Naïve, treatment-naïve; SVR, sustained virological response; Null, null response; wk, weeks

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Addendum

After submission of this work, two papers were published on interferon-free regimens.[55,56]

Conflict of interest

Dr. Kanda reports receiving lecture fees from Chugai Pharmaceutical, MSD, Tanabe-Mitsubishi, Ajinomoto, Bristol-Myers Squibb, and GlaxoSmithKline, and Prof. Yokosuka reports receiving grant support from Chugai Pharmaceutical, Bayer, MSD, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, and Bristol-Myers Squibb.

Author contributions

Drafting the manuscript (TK), discussion and approval of the manuscript (TK, SN, MN, XJ, TM, SW, OY).

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