Acta Pharmaceutica Sinica B 2016;6(1):26–31

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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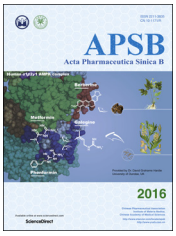

REVIEW

Direct anti-HCV agents

Xingquan Zhang*

Division of Infectious Diseases, University of California, San Diego School of Medicine, La Jolla, CA 92093, USA

Received 1 July 2015; received in revised form 15 July 2015; accepted 24 August 2015

KEY WORDS

Hepatitis C virus;
Cure HCV;
Sustained virologic response;
Direct antiviral agents;
NS3/4A protease inhibitor

Abstract Unlike human immunodeficiency virus (HIV) and hepatitis B virus (HBV), hepatitis C virus (HCV) infection is a curable disease. Current direct antiviral agent (DAA) targets are focused on HCV NS3/4A protein (protease), NS5B protein (polymerase) and NS5A protein. The first generation of DAAs includes boceprevir and telaprevir, which are protease inhibitors and were approved for clinical use in 2011. The cure rate for genotype 1 patients increased from 45% to 70% when boceprevir or telaprevir was added to standard PEG-IFN/ribavirin. More effective and less toxic second generation DAAs supplanted these drugs by 2013. The second generation of DAAs includes sofosbuvir (Sovaldi), simeprevir (Olysio), and fixed combination medicines Harvoni and Viekira Pak. These drugs increase cure rates to over 90% without the need for interferon and effectively treat all HCV genotypes. With these drugs the "cure HCV" goal has become a reality. Concerns remain about drug resistance mutations and the high cost of these drugs. The investigation of new HCV drugs is progressing rapidly; fixed dose combination medicines in phase III clinical trials include Viekirax, asunaprevir+daclatasvir+beclabuvir, grazoprevir+elbasvir and others.

*E-mail address: xiz002@ucsd.edu

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2015.09.008

1. Introduction

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). HCV is a positive-strand RNA virus encoding a polyprotein that undergoes proteolytic cleavage to 10 polypeptides, each with a distinct function. The structural proteins consist of two envelope glycoproteins, both of which are targets of the host antibody response, and the core protein, which interacts with progeny viral genomes for assembly of the virus. The nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B form a complex with viral RNA to initiate viral replication in a cytoplasmic membranous structure[1].

HCV causes both acute and chronic infections. Acute infection is a non-life threatening disease and ranges from being asymptomatic to causing a self-limited hepatitis. About 15%–45% of acute infected patients spontaneously clear HCV within several months after infection. The remaining 55%–85% of patients develop chronic infection. Currently, almost 140 million people in the world have chronic HCV infection, including 4 million Americans and over 10 million Chinese. Of those with chronic infection, 15%–30% develop cirrhosis and the risk of hepatocellular carcinoma increases more than 20 fold within 20 years of infection. Unlike hepatitis A and B, a vaccine for HCV is not available. The therapy for HCV infection relies only on antiviral drugs. Before 2011, the standard regimen of anti-HCV therapy was pegylated interferon alpha (PEG-IFNα) plus ribavirin (RBV) for a period of 24–48 weeks. This dual therapy (DT) produced cure rates of between 70%–80% for HCV genotypes 2 and 3, and 45%–60% for genotypes 1 and 4. Although some patients could be cured of their infection, this DT regimen was associated with substantial toxicity and many patients were not candidates for therapy because of contraindications to interferon including pre-existing depression and certain auto-immune diseases. These toxicities and contraindications combined with low response rates (especially in genotype 1 and 4 infection) drove a search for more effective and less toxic agents. Over the last several years, basic HCV research has led to the discovery and clinical development of a large number of new anti-HCV drugs, including several direct-acting antivirals that are targeted against several molecular targets. These include NS3/4A protease inhibitors (PIs), NS5B polymerase inhibitors and NS5A inhibitors.

The first generation of NS3/4A PIs (boceprevir and telaprevir) was approved for clinical use in 2011. In the middle of 2011, PEG-IFN/RBV therapy for HCV genotype 1 infection was supplanted by PEG-IFN–based triple therapies with the addition of first generation PIs—boceprevir (BOC) or telaprevir (TVR). With the addition of boceprevir or telaprevir to PEG-IFN/RBV, cure rates for HCV genotype 1 increased to 65%–75%. By 2013, the second generation of DAA drugs including sofosbuvir increased sustained virologic response (SVR) rates to 90%–100%. A "second generation" PI, simprevir, resulted in similar SVR rates when added to PEG-IFN/RBV. By 2014, IFN-free regimens had essentially replaced interferon-based therapy. Sofosbuvir/ledipasvir and sofosbuvir/simeprevir/RBV resulted in genotype1 SVR rates of 92%–100%. Combinations of ombitasvir, paritaprevir/ritonavir/dasabuvir with/without RBV achieved SVR rates as high as 100%. The next steps in the clinical development of anti-HCV therapy are expected by late 2015–early 2016 with the availability of pangenotypic ultra-rapid (4–8 weeks) single pill regimens such as grazoprevir/MK8742, Sofosbuvir/GS5816 and BMS791325/DAC/Asunaprevir. This review is focused on the development of the above-mentioned DAA drugs (Table 1) in the treatment of HCV infections in next several years.

Table 1 DAAs in clinical use and in phase III trials.

Generic name	Brand name	Mechanism	Status	Pharmaceutical company
Boceprevir	Victrelis	NS3/4A protease	Approved in 5/2011, to be discontinued in 12/2015	Merck
Telaprevir	Incivek	NS3/4A protease	Approved in 5/2011, discontinued in 10/2014	Vertex
Simeprevir	Olysio	NS34A protease	Approved in 10/2013	Janssen and MEDIVIR ab
Sofobuvir	Sovaldi	NS5B polymerase	Approved in 12/2013	Gilead Science
Sofobuvir (GS-7977) +Ledipasvir (GS-5855)	Harvoni	NS5B polymerase +NS5A proteain	Approved in 10/2014	Gilead Sciences
Ombitasvir (ABT-267) +Paritaprevir (ABT-450) +Ritonavir +Dasabuvir (BT-333))	Viekira Pak	NS5A protein +NS3/4A protease +a cytochrome P450 3A4 inhibitor +NS5B polymerase	Approved in 12/2014	AbbVie
Asunaprevir (BMS-650032) +Daclatasvir (BMS-790052) +Beclabuvir (BMS-791325)	n/a	NS3/4A protease +NS5A protein +NS5B polymerase	Phase III	Bristol-Myers Squibb
Grazoprevir (MK-5172) +Elbasvir (MK-8742)	n/a	NS3/4A protease +NS5A protein	Phase III	Merck
Ombitasvir (ABT-267) +Paritaprevir (ABT-450) +Ritonavir	Viekirax	NS5A protein +NS3/4A protease +a cytochrome P450 3A4 inhibitor	Phase III	Abb Vie

n/a, not available.

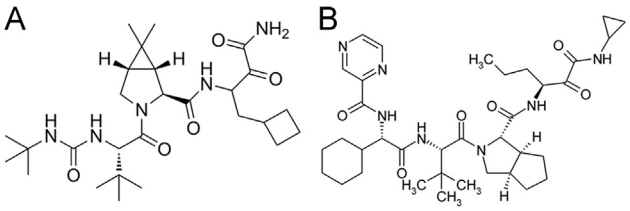

Figure 1 Structures of (A) boceprevir and (B) telaprevir.

2. First generation DAAs: boceprevir and telaprevir

Boceprevir (SCH 503034, Fig. 1A)[2,3] and telaprevir (VX-950, Fig. 1B)[4,5] are HCV NS3/4A PIs. Both of these drugs show potent inhibition of the HCV NS3/4A protease with K_i values of 14 and 7 nmol/L, respectively. They also exhibit ant-HCV activity in cell culture with IC_{50} values of 200–280 nmol/L. In phase I clinical trials, treatment with either boceprevir or telaprevir resulted in 1.5–4.4 $\log_{10}$ IU/mL drops in plasma HCV RNA levels. Combining boceprevir or telaprevir with PEG-IFNα with or without RBV increased anti-HCV effects and decreased the emergence of resistance. The results of phase III trials demonstrated that triple therapy with either boceprevir or telaprevir and PEG-IFNα and RBV increased SVR rates from 30%–40% with PEG-IFNα and RBV alone to 65%–76%. Although the two drugs were reasonably well tolerated the continued presence of PEG-IFNα and RBV in the combination regimen severely limited their clinical utility. When clinical studies of the two drugs were completed, the US Food and Drug Administration (FDA) approved boceprevir (trade name: Victrelis) and telaprevir (trade name: Incivek, Incivo) for use in combination with PEG-IFNα and RBV for adult patients chronically infected with HCV genotype 1 in May of 2011. Since 2011, more than 100,000 people globally have taken the two drugs. Vertex Pharmaceuticals decided to stop selling Incivek on October 16, 2014. Merck plans to discontinue selling boceprevir for HCV infection by December 2015. These decisions were based on the appearance of the new and better next generation DAAs that will be described in more detail below. These new drugs can be used in well tolerated all oral, interferon-free regimens, such as sofosbuvir/ledipasvir (Harvoni, Gilead) and Viekira Pak (AbbVie). These regimens produce cure rates in the 90%–100% range when taken for 8–24 weeks.

3. Second generation DAAs

3.1. *Sofosbuvir*

Sofosbuvir (GS-7977, Fig. 2A)[6,7] is a nucleotide analog that inhibits HCV NS5B polymerase. After ingestion, it is rapidly converted to GS-331007. GS-331007 is efficiently taken up by hepatocytes and become GS-461203, the pharmacologically active uridine analog 5'-triphosphate form after conversion by cellular kinases. This triphosphate compound mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA polymerase into the elongating RNA primer strand, resulting in chain termination. Sofosbuvir displays potent inhibitory activity against HCV RNA replication with an EC_{50} of 0.92 nmol/L and EC_{90} of 0.29 μmol/L. When assessed in an 8-day cytotoxicity assay, it shows no cytotoxicity against Huh7, HepG2 and CEM cells even at concentrations up to 100 μmol/L. In clinical trials of sofosbuvir/PEG-IFN/RBV, patients with genotype 1 or 4 infection achieved SVR rates of 92%. The combination of sofosbuvir and RBV achieved SVR rates of 100% for genotype 2 infection and 91% for genotype 3 infection. Because GS-461203 does not inhibit host DNA polymerases, RNA polymerases or mitochondrial RNA polymerases, sofosbuvir is extremely well tolerated by patients. On December 6, 2013, FDA approved sofosbuvir (brand name: Sovaldi) for use in the treatment of chronic hepatitis C, genotypes 1, 2, 3 and 4, in combination with PEG-IFN and RBV, or with RBV alone (depending on the genotype). Subsequently it has been approved for use in combination with the viral NS5A inhibitor ledipasavir in an interferon-free regimen for the treatment of genotype 1 patients. Sofosbuvir is also highly effective in HCV patients who are co-infected with HIV.

3.2. *Simeprevir*

Simeprevir (TMC435, Fig. 2B)[8,9] is a highly specific and potent inhibitor of HCV NS3/4A protease. K_i values of 0.5 and 0.4 nmol/L against the protease enzyme were determined in biochemical assays. The EC_{50} of simeprevir for inhibiting HCV genotypes 1b and 1a in cell culture models of HCV infection is 8 nmol/L. The selectivity index is over 5000. Simeprevir is extensively distributed to the liver and intestinal tract with a biovailability of 44% after a single oral administration. Clinical results demonstrate that simeprevir is safe and well tolerated, and achieved SVR rate (viral cure) of 79%–81% in three pivotal phase III combination trials in hepatitis C-infected patients. Semeprevir was also studied in interferon-free trials with and without ribaviran. An SVR rate of 92% was achieved when it was used in combination with sofosbuvir in genotype 1 patients. On October 24, 2013, FDA approved simeprevir (trade name: Olysio, Sovriad) for clinical use, and it is indicated for treating chronic HCV infection as a part of a triple antiviral treatment regimen consisting of two other drugs: PEG-IFN and RBV. It is primary efficacious in treating HCV genotype 1 infected subjects with compensated liver disease, including cirrhosis. Simeprevir has been tested in interferon-free regimens with other direct-acting antiviral agents including daclatastir and sofosbuvir. A recent study has shown the effectiveness of simeprevir therapy with PEG-IFN and RBV in post-liver transplant patients with recurrent HCV.

3.3. *Harvoni*

Harvoni (sofosbuvir+ledipasvir; GS7977+GS-5855) is a fixed-dose combination tablet containing ledipasvir (90 mg) and sofosbusvir (400 mg) for oral administration. As mentioned above, sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase. Ledipasvir (Fig. 2C)[10] is an HCV NS5A inhibitor. In HCV replicon assays, the EC_{50} values against genotypes 1a and 1b are 0.031 and 0.004 nmol/L, respectively. The median EC_{50} values against chimeric replicons are 0.018 and 0.006 nmol/L for genotypes 1a and 1b. Ledipasvir has lower antiviral activity

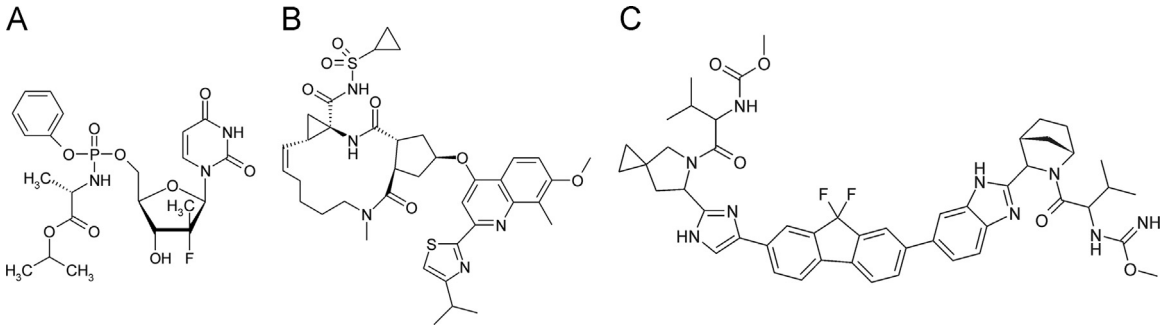

Figure 2 Structures of (A) sofosbuvir (GS-7977), (B) simeprevir (TMC435) and (C) ledipasvir.

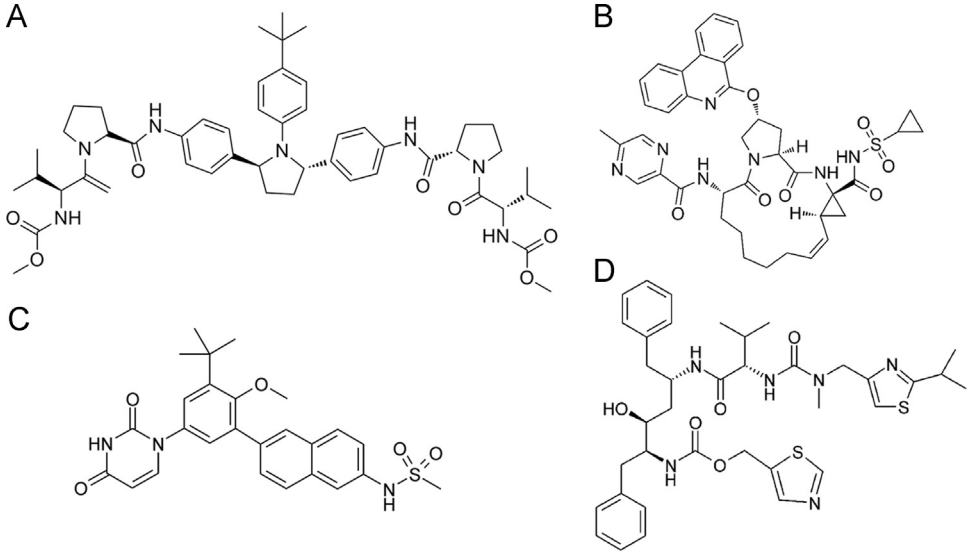

Figure 3 Structures of (A) ombitasvir, (B) paritaprevir, (C) dasabuvir and (D) ritonavir.

compared to genotype 1 against genotypes 4a, 5a and 6a with EC_{50} values of 0.39, 0.15 and 1.1 nmol/L, respectively. Ledipasvir also exhibits substantially lower activity against genotypes 2a, 2b, 3a, and 6e with EC_{50} values of 21–249, 16–530, 168, and 264 nmol/L, respectively. The efficacy of Harvoni against HCV genotype 1 was demonstrated in three phase III trials in which SVR rates of 93%–99% were achieved after 12 weeks of therapy. Relapse rates of 0–2% were observed depending on baseline HCV RNA levels, with or without liver cirrhosis and other factors[11]. The US FDA approved Harvoni to treat chronic HCV genotype 1 infection on October 10, 2014.

3.4. *Viekira Pak*

Viekira Pak contains three new drugs—ombitasvir (Fig. 3A), paritaprevir, (Fig. 3B), dasabuvir (Fig. 3C) and ritonavir (Fig. 3D), a previously approved drug which is used to increase blood levels of paritaprevir. Viekira Pak can be used with or without RBV, but it is not recommended for patients with poor liver function (decompensated cirrhosis).

Ombitasvir (Fig. 3A)[12] is an HCV NS5A inhibitor with picomolar potency, pan-genotypic activity, and EC_{50} values of 0.82–19.3 pmol/L against HCV genotypes 1 through 5 and 366 pmol/L against genotype 6a. Ombitasvir's *in vivo* activity was demonstrated in an a 3-day monotherapy study at 5, 25, 50 and 200 mg dosed once daily in which decreases in HCV RNA of up to 3.1 $\log_{10}$ IU/mL were observed. Paritaprevir (Fig. 3B)[13] is an efficacious inhibitor of HCV NS3/4A protease, with EC_{50} values of 1.0, 0.21, 5.3, 19, 0.09 and 0.69 nmol/L against stable HCV replicons with NS3 protease from genotypes 1a, 1b, 2a, 3a, 4a, and 6a, respectively. In a 3-day monotherapy study with HCV genotype 1-infected patients, paritaprevir was co-administered with ritonavir (Fig. 3D[14], a cytochrome P450 3A4 inhibitor that is required as a pharmacologic enhancer for paritaprevir). In this study a mean maximum plasma HCV RNA decline of 4.02 $\log_{10}$ IU/mL was observed. Dasabuvir (Fig. 3C)[15] is a nonnucleoside HCV polymerase inhibitor with EC_{50} values of 2.2 and 7.7 nmol/L against HCV genotypes Type 1a and 1b, respectively. In combination studies with other Abbvie DAA drugs comprising Viekera Pak, 91%–100% of patients were cured including those considered difficult to treat. The recommended dosing for Viekira Pak is two ombitasvir, paritaprevir, ritonavir 12.5 mg/75 mg/50 mg tablets once daily and one dasabuvir 250 mg tablet twice daily[16]. The FDA approved Viekira Pak to treat patients with HCV genotype 1 infection, including those with a type of advanced liver disease called cirrhosis on December 19, 2014.

4. Investigational new drugs in phase III trials

Currently, several new drugs have entered into phase III clinical trials, but have not been approved by FDA to use in clinical.

4.1. *Asunaprevir+daclatasvir+beclabuvir*

Asunaprevir (BMS-650032, Fig. 4A)[17] is a HCV NS3 protease inhibitor, and it has K_i values of 0.4 and 0.24 nmol/L against HCV genotypes 1a and 1b protease and IC_{50} values of 0.7, 0.3, 15, 78, 320, 1.6, 1.7 and 0.9 nmol/L for genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a and 6a. Daclatasvir (BMS-790052, Fig. 4B)[18] inhibits the HCV nonstructural protein NS5A. Recent research suggests that it targets two steps of the viral replication process, enabling rapid decline of HCV RNA. Daclatasvir inhibited the JFH-HCV 3a hybrid replicons with EC_{50} ranging from 120 to 870 pmol/L, and similar daclatasvir potencies were also observed with replicon cell lines (EC_{50}=0.14–1.25 nmol/L). Beclabuvir (BMS-791325, Fig. 4C)[19] is a non-nucleoside inhibitor of HCV NS5B polymerase. It inhibits genotype 1 HCV NS5B polymerase with nanomolar potency, but shows no activity against the closely related RNA-dependent RNA polymerase from the pestivirus, bovine viral diarrhea virus, or human DNA polymerase. The clinical study that evaluated cirrhotic patients in a 12-week regimen of this three drug fixed combination regimen showed SVR 12 rates of 98% of in treatment-naïve and 93% in treatment-experienced cirrhotic patients with RBV and 93% of treatment-naïve and 87% of treatment-experienced cirrhotic patients without RBV[20].

4.2. *Grazoprevir+elbasvir*

Grazoprevir (MK-5172, Fig. 5A)[21,22] is selective inhibitor of HCV NS3/4A protease with broad activity across genotypes and resistant variants. In the replicon assay, it demonstrated sub-nanomolar to low-nanomolar EC_{50} values against genotypes 1a, 1b and 2a, and no evidence for cellular cytotoxicity. Grazoprevir was administered orally (1 mg/kg twice daily for 7 days) to three chimpanzees infected by wild-type genotype 1a or 1b HCV with viral titers 10^4–10^6 IU/mL, and all animals experienced an immediate, profound reduction in plasma HCV RNA levels (4–5 $\log_{10}$ IU/mL). Elbasvir (MK-8742, Fig. 5B)[23,24] interferes with the HCV protein NS5A. In laboratory experiments with cells and HCV, it is active against most strains of HCV, including genotypes 1a, 1b, 2a, 3a and 4a. Side effects are similar to those reported for grazoprevir. High SVR rates were achieved with combinations of these drugs in patients with HCV infection, Grazoprevir+elbasvir+RBV resulted in a SVR_{12} rate of, 93% in patients with HCV monoinfection and, 98% in patients who were co-infected with HIV. In another study grazoprevir+elbasvir+RBV resulted in an SVR_{12} rate of, 97%. Without RBV grazoprevir+elbasvir resulted in a SVR_{12} rate of 87%. SVR_{12} rates were similar whether or not patients had HCV genotype 1a (92%) or genotype 1b (95%).

4.3. *Viekirax (ombitasvir+paritaprevir+ritonavir)*

In the Viekirax tablet[25], the dosages of ombitasvir, paritaprevir, ritonavir are increased from 12.5 to 25 mg, 75 to 150 mg and 50 to 100 mg, respectively. On January 16, 2015, the European Medicines Agency has approved Viekirax and Exviera (Asunaprevir, 250 mg, twice daily) with or without RBV for patients with chronic HCV genotype 1 infections, including those with compensated liver cirrhosis, HIV-1 co-infection, patients on opioid substitution therapy and liver transplant recipients. Additionally, Viekirax has been approved for use with RBV in genotype 4 chronic hepatitis C patients. Despite cure rates of 97%, FDA has not yet approved Viekirax for clinical use. AbbVie has presented late-breaking, preliminary phase IIIb data with Viekirax+Exviera in chronic hepatitis C patients with renal impairment

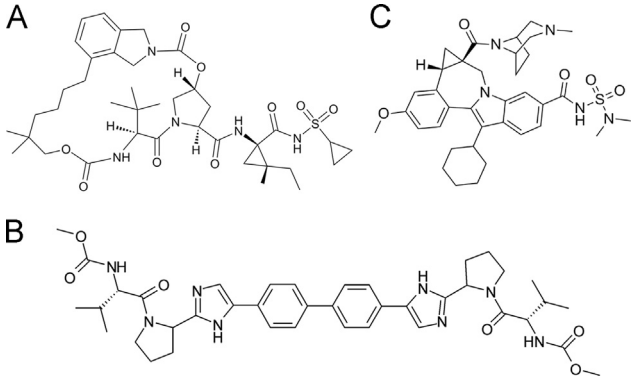

Figure 4 Structures of (A) asunaprevir, (B) daclatasvir and (C) beclabuvir.

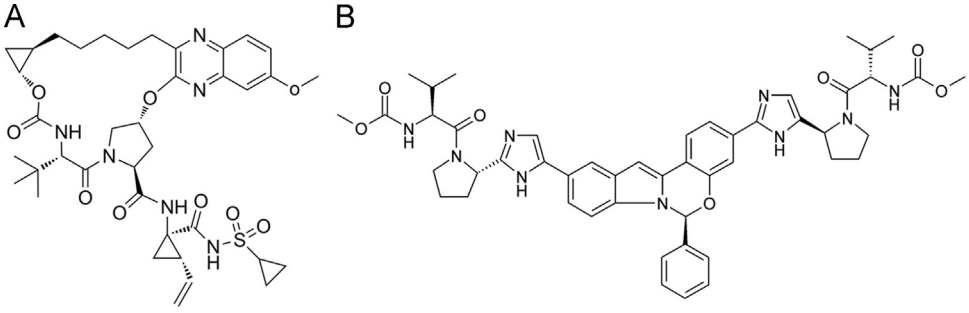

Figure 5 Structures of (A) grazoprevir and (B) elbasvir.

at the International Liver Congress 2015 on April 25, 2015, and hopes to get approval from FDA soon[25].

5. Conclusions

DAA's have changed the landscape of HCV therapy. The first generation HCV PIs began the new era of anti-HCV therapeutics, but within two years, they were replaced by new and better DAAs. With the second generation of DAAs "HCV cure" can be promised to 95%–100% of patients. This generation of drugs is expensive but new pricing strategies for resource limited countries are expected to make these drugs available globally over the next several years. Even better DAAs under investigation will go to market soon. It is the dawn of a new era of therapy for HCV infected persons around the world.

Acknowledgment

The editorial assistance of Dr. Robert Schooley is gratefully acknowledged.

References

1. Ashfaq UA, Javed T, Rehman S, Nawaz Z, Riazuddin S. An overview of HCV molecular biology, replication and immune responses. *Virol J* 2011;**8**:161–70.
2. Siliva MO, Treitel M, Graham DJ, Curry S, Frontera MJ, Mcmonagle P, et al. Antiviral activity of boceprevir monotherapy in treatment-naïve subjects with chronic hepatitis C genotype 2/3. *J Hepatol* 2013;**59**:31–7.
3. Kwo PY. Boceprevir: a novel nonstructural 3 (NS3) protease inhibitor for the treatment of chronic hepatitis C infection. *Ther Adv Gastroenterol* 2012;**5**:179–88.
4. Lin T-I, Lenz O, Fanning G, Verbinnen T, Delouvroy F, Scholliers A, et al. *In vitro* activity and preclinical profile of TMC435350, a potent hepatitis C virus protease inhibitor. *Antimicrob Agents Chemother* 2009;**53**:1377–85.
5. Cunningham M, Foster GR. Efficacy and safety of telaprevir in patients with genotype 1 hepatitis C infection. *Ther Adv Gastroenterol* 2012;**5**:139–51.
6. Rodriguez-Torres M, Lawitz E, Kowdley KV, Nelson DR, DeJesus E, McHutchison JG, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. *J Hepatol* 2013;**58**:663–8.
7. Lam AM, Espiritu C, Bansal S, Micolochick Steuer HM, Niu C, Zennou V, et al. Genotype and subtype profiling of PSI-7977 as a nucleotide inhibitor of hepatitis C virus. *Antimicrob Agents Chemother* 2012;**56**:3359–68.
8. Lenz O, Verbinnen T, Lin TI, Vijgen L, Cummings MD, Lindberg J, et al. *In vitro* resistance profile of the hepatitis C virus NS3/4A protease inhibitor TMC435. *Antimicrob Agents Chemother* 2010;**54**:1878–87.
9. Jacobson IM, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, et al. Simeprevir with pegylated interferon α 2a plus ribavirin in treatment-naïve patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014;**384**:403–13.
10. Link JO, Taylor JG, Xu L, Michell M, Guo H, Liu H, et al. Discovery of ledipasvir (GS-5885): a potent, once-daily oral NS5A inhibitor for the treatment of hepatitis C virus infection. *J Med Chem* 2014;**57**:2033–46.
11. Osinusi A, Townsend K, Kohli A, Nelson A, Seamon C, Meissner EG, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA* 2015;**313**:1232–9.
12. Krishnan P, Beyer J, Mistry N, Koev G, Reisch T, DeGoey D, et al. *In vitro* and *in vivo* antiviral activity and resistance profile of ombitasvir, an inhibitor of hepatitis C virus NS5A. *Antimicrob Agents Chemother* 2015;**59**:979–87.
13. Pilot-Matias T, Tripathi R, Cohen D, Gaultier I, Dekhtyar T, Lu LJ, et al. *In vitro* and *in vivo* antiviral activity and resistance profile of the hepatitis C virus NS3/4A protease inhibitor ABT-450. *Antimicrob Agents Chemother* 2015;**59**:988–97.
14. Kati W, Koey G, Irvin M, Beyer J, Liu Y, Krishnan P, et al. *In vitro* activity and resistance profile of dasabuvir, a nonnucleoside hepatitis C virus polymerase inhibitor. *Antimicrob Agents Chemother* 2015;**59**:1505–11.
15. Sulkowski MS, Eron JJ, Wyles D, Trinh R, Lalezari J, Wang C, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA* 2015;**313**:1223–31.
16. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014;**147**:359–65.
17. Scola PM, Sun LQ, Wang AX, Chen J, Sin N, Venables BL, et al. The discovery of asunaprevir (BMS-650032), an orally efficacious NS3 protease inhibitor for the treatment of hepatitis C virus infection. *J Med Chem* 2014;**57**:1730–52.
18. Wang CF, Jia LL, Qiu DK, Valero L, Huang X, Sun JH, et al. *In vitro* activity of BMS-790052 on hepatitis C virus genotype 4 NS5A. *Antimicrob Agents Chemother* 2012;**56**:1588–90.
19. Lemm JA, Liu M, Gentles RG, Ding M, Voss S, Pelosi LA, et al. Preclinical characterization of BMS-791325, an allosteric inhibitor of hepatitis C virus NS5B polymerase. *Antimicrob Agents Chemother* 2014;**58**:3485–95.
20. Muir AJ, Poordad F, Lalezari J, Everson G, Dore GJ, Herring R, et al. Daclatasvir in combination with asunaprevir and beclabuvir for hepatitis C virus genotype 1 infection with compensated cirrhosis. *JAMA* 2015;**313**:1736–44.
21. Summa V, Ludmerer SW, McCauley JA, Fandozzi C, Burlein C, Claudio G, et al. MK-5172, a selective inhibitor of hepatitis C virus NS3/4a protease with broad activity across genotypes and resistant variants. *Antimicrob Agents Chemother* 2012;**56**:4161–7.
22. Coburn CA, Meinke PT, Chang W, Fandozzi CM, Graham DJ, Hu B, et al. Discovery of MK-8742: an HCV NS5A inhibitor with broad genotype activity. *ChemMedChem* 2013;**8**:1930–40.
23. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Guyarder D, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. *Lancet* 2015;**385**:1075–86.
24. Sulkowski MS, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of MK-5172+MK-8742±ribavirin in HCV mono-infected and HIV/HCV co-infected treatment-naïve, non-cirrhotic patients with hepatitis C virus genotype 1 infection: the C-WORTHY study (final results, parts A and B). In: *Proceedings of the 65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD)*. 7–11 Nov. Boston, US: AASLD; 2014.
25. Abb Vie presents late-breaking, preliminary phase 3b data with VIEKIRAX® + EXVIERA® in chronic hepatitis C patients with renal impairment at the International Liver Congress ™ 2015. Vienna, Austria; 25 April 2015.