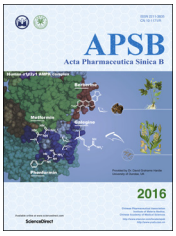
Acta Pharmaceutica Sinica B 2016;6(1):26–31

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

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



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.