



2016 Hepatitis C virus: Global view

Hepatitis C virus: Promising discoveries and new treatments

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Abstract

Despite advances in therapy, hepatitis C virus (HCV) infection remains an important global health issue. It is estimated that a significant part of the world population is chronically infected with the virus, and many of those affected may develop cirrhosis or liver cancer. The virus shows considerable variability, a characteristic that directly interferes with disease treatment. The response to treatment varies according to HCV genotype and subtype. The continuous generation of variants (quasispecies) allows the virus to escape control by antivirals. Historically, the combination of ribavirin and interferon therapy has represented the only treatment option for the disease. Currently, several new treatment options are emerging and are available to a large part of the affected population. In addition, the search for new substances with antiviral activity against HCV continues, promising future improvements in treatment. Researchers should consider the mutation capacity of the virus and the other variables that affect treatment success.

Key words: Hepatitis C infection; Hepatitis C virus; Treatments; Antiviral research

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Core tip: In recent years, new treatments for hepatitis C have been approved and represent a major advancement in this field. However, there are limitations that should be considered, and research for new treatments must continue. The objective of this review is to demonstrate the breakthroughs that have occurred and to discuss future developments.

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INTRODUCTION

Hepatitis C virus (HCV) infection is an important cause of cirrhosis and hepatocellular carcinoma worldwide^[1-3]. It is very dangerous due to the breakthrough of long-term asymptomatic HCV^[4].

HCV is transmitted through exposure to infected blood and blood products. HCV infection can be spread through blood transfusion, injection drug use, sexual intercourse, surgery, and tattooing^[2,5]. HCV infection is defined as the presence of HCV RNA and anti-HCV antibodies in the serum or plasma; a positive HCV antibody test indicates exposure to HCV and could represent a current or past infection. A positive HCV RNA test indicates a current HCV infection^[2].

It is estimated that 130-150 million people globally have chronic hepatitis C infection, and a significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. According to the World Health Organization, 350000 to 500000 people die each year from hepatitis C-related liver diseases. The most affected regions are Central and East Asia and North Africa, although the virus is found worldwide^[6].

The natural history of HCV is influenced by a wide variety of factors. Host factors include age at infection, gender, race, obesity, steatosis, insulin resistance/diabetes, genetics, alanine aminotransferase levels and exercise. Viral factors include HCV RNA level, quasispecies/genotype, coinfection with hepatitis B virus and coinfection with human immunodeficiency virus. Environmental factors include alcohol use, cigarette use, cannabis use, caffeine consumption and herbal product use^[1].

Approximately 15%-45% of infected persons spontaneously clear the virus within 6 mo of infection without any treatment, and the remaining 55%-85% of persons may progress to persistent chronic infection. It is estimated that the risk of developing cirrhosis of the liver within 20 years is 15%-30% in those with chronic HCV infection^[6], and the risk of developing hepatocellular carcinoma is 1%-4% per year^[1].

Acute HCV hepatitis in immunocompetent individuals is generally asymptomatic, but immunocompromised hosts (HIV infection) experience lymphoplasmatic portal inflammation, interface hepatitis, necroinflammatory lobular changes, moderately advanced fibrosis or rapid progression to fibrosis over a period of time^[7].

Chronic hepatitis is defined as the persistence of infection for at least 6 mo after the onset of infection and is characterized by necroinflammation accompanied by a variable degree of fibrosis^[7], end-stage liver

disease and hepatocellular carcinoma^[1].

The main extrahepatic manifestations in patients with HCV infection are immune- and inflammatory-related. Immune-related extrahepatic manifestations include mixed cryoglobulinemia, cryoglobulinemic vasculitis, B-cell NHL, Sicca syndrome, arthralgia/myalgia, autoantibody production (*i.e.*, cryoglobulins, rheumatoid factor, and antinuclear, anticardiolipin, antithyroid and anti-smooth muscle antibodies), polyarthritis nodosa, monoclonal gammopathies, and immune thrombocytopenia. Inflammatory-related extrahepatic manifestations consist of type 2 diabetes mellitus, insulin resistance, glomerulonephritis, renal insufficiency, fatigue, cognitive impairment, depression, impaired quality of life, polyarthritis/fibromyalgia, and cardiovascular disorders (*i.e.*, stroke and ischemic heart disease)^[8]. Recent studies have suggested that HCV infection leads to increased risk of developing cardiovascular diseases and has been linked to increased risk of mortality caused by these diseases^[9].

Several studies have considered the existence of occult HCV infection (viral RNA identified in hepatocytes but absent in serum). Although occult HCV infection is challenged by some researchers and is characterized by others as a milder condition than chronic hepatitis C, it is necessary to consider its existence because some studies have shown links between occult HCV infection and liver cirrhosis and hepatocellular carcinoma. In addition, due to the emergence of new treatment options, all possibilities should be considered, and special attention should be given to transfusion centers and patient risk groups^[10,11].

HCV

HCV, classified in the family *Flaviviridae*, is an enveloped, single stranded positive sense RNA virus with a genome approximately 9600 nucleotides in length^[12], encoding approximately 3000 amino acids^[13]. Most of the genome is composed of a single open reading frame that encodes ten proteins: three structural proteins (core, E1, E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B)^[13]. Most recently, an HCV protein named F was reported^[14,15].

The most variable region of the genome is the region that codes the membrane glycoproteins E1 and E2^[16]. Within the E2 gene, two hypervariable regions (HVR1 and HVR2) are described that show less sequence homology between isolates, with 50% identity^[17]. Non-structural protein genes, such as the core gene, are some of the most conserved on the genome^[12]. Within the 5'-NCR region, the most distant related isolates present 90% sequence identity^[18,19].

The host immune system, large population sizes, short generation times and high replication rates are the factors that lead to the genetic variability

of HCV^[20]. Seven genetic lineages (genotypes 1 to 7) are recognized. These genotypes are subdivided into closely related sub-types differing from each other by 15% in nucleotide sequences^[21]. Differences between the complete genomes occur at 31%-33% of nucleotide sites^[22]. In Western countries, subtypes 1a, 1b and 3a are believed to cause the majority of HCV infections and are widely distributed^[12].

For example, only 10%-20% of patients chronically infected with HCV genotype 1 show complete and permanent disappearance of the virus when treated with IFN- α alone, and 40%-50% experience successful treatment when treated with a combined therapy (INF- α /RBV). When patients infected with genotypes 2 or 3 are treated with monotherapy or combined therapy, higher successful treatment rates are observed (50% and 70%-80%, respectively)^[23,24].

The mutation rate of HCV is estimated to be 2.5×10^{-5} mutations per nucleotide per genome replication^[25], which is one of the highest rates for RNA viruses, including retroviruses^[26]. Recombination also increases the genetic variability of HCV. Inter and intra genotypic recombinations have already been reported in various geographic locations, and the existence of intergenotypic recombination forms has also been reported^[27,28]. Genotype 2 is considered to be present in most of the cases of recombinant forms, but other genotypes, except for genotype 4 and 7, also exhibit recombinant forms^[29]. At the same time, the mutation rate may negatively affect the viability of viral populations. In a situation called lethal mutagenesis, a nucleotide sequence loses its information when the error rate transcends a tolerable limit^[30].

Due to the high replication rate of HCV, an extensive number of variants are continuously produced during infection. These variants are closely related to each other but differ in nucleotide sequence, circulating as a complex population known as quasispecies. This population is able to rapidly adapt to a constantly changing environment^[31,32]. This adaptation could lead to the coexistence of diverse variants in infected patients, creating an environment for intra and inter quasispecies interactions^[33]. As a result of the continuous generation of variants, some of the variants may adapt to this changing environment and escape control by antiviral drugs^[34]. Predominant and minor quasispecies can be transmitted in humans^[35,36] and experimentally infected chimpanzees^[37,38]. It is important to highlight that the HCV population fluctuates in patients during therapy, suggesting that HCV quasispecies may follow different evolution paths in different patients^[39].

Host genetics are also indicated as a factor that could influence HCV evolution and treatment response^[40]. For example, single nucleotide polymorphisms near the IL-28B gene appear to be associated with a low genetic variability in the NS3 coding region of the HCV genome^[41].

EVOLUTION OF HCV TREATMENT

Since HCV treatment began in the early 1990s, treatment options have improved. Interferon alpha (IFN- α) was the first pan-genotypic option, with sustained virologic response (SVR) rates of 8%-21%^[42]. Subsequently, the guanosine analogue ribavirin (RBV) was combined with IFN- α , which enhanced SVR rates to 40%. Then, pegylated IFN- α (PEG-IFN- α) associated with RBV improved SVR rates from 42% to 52%^[43-45]. In 2011, the first wave of direct-acting antiviral agents (DAAs), NS3/4A protease inhibitors telaprevir (TVR) and boceprevir (BOC), became available. The association of these protease inhibitors with PEG-IFN- α /RBV improved SVR rates among patients with HCV genotype 1 infection. In treatment-naïve patients, the addition of TVR or BOC to PEG/RBV leads to an SVR increase of approximately 30%. Despite this improvement in SVR, these drugs were associated with serious adverse events (AEs) and low tolerance. More recently, a second wave of new DAAs allowed IFN-free, highly effective regimens. SVR can be achieved in more than 90% of treated patients *via* IFN-free regimens, with minimal AEs and high tolerability^[46-49]. Unlike the nonspecific IFN- α -based and PEG-IFN- α -based therapies, DAAs target various proteins involved in HCV replication. In addition, most of these agents are specific to one or more genotypes. The classes of DAAs include NS3/4A protease inhibitors, NS5A inhibitors (nucleotides and non-nucleotide analogues), and NS5B polymerase inhibitors. During HCV replication, NS3/4A serine protease is required for self-cleavage, the NS5A region plays an important role in viral replication and assembly, and the NS5B region encodes RNA polymerase. Some of these drugs were initially combined with PEG-IFN- α and RBV, including the protease inhibitors TVR, BOC and simeprevir (SMV) and the NS5B polymerase inhibitor sofosbuvir (SOF). However, these regimens were still associated with PEG-IFN- α and RBV AEs and low tolerability^[50-52].

All-oral treatment options followed this development, some associated with RBV and some not, including the combinations of SMV and SOF and SOF and NS5A inhibitor daclatasvir, the 3D regimen (paritaprevir/ritonavir/ombitasvir, co-administered with dasabuvir), and SOF plus ledipasvir. In recent years, more drugs have been designed, including grazoprevir, elbasvir, asunaprevir, beclabuvir, faldaprevir, and deleobuvir^[52,53]. Drug options and their respective mechanisms and genotype sensitivity are shown in Table 1. The combined therapies increased SVR rates and tolerability and shortened treatment duration^[52]. Treatment options for HCV infection, ranging from IFN-based regimens to new all-oral combinations, are presented in Table 2.

Although HCV treatment has clearly improved since the introduction of DAAs, some challenges remain. Some populations remain difficult to treat, such as cirrhotic patients, prior non-responders, genotype 3-infected patients and patients with renal

Table 1 Drugs for hepatitis C virus treatment

Mechanism of action	Drug	Genotype
Protease inhibitor	Telaprevir	1
	Boceprevir	1
	Simeprevir	1
	Paritaprevir	1, 4
	Grazoprevir	1, 4
	Asunaprevir ¹	1
	ABT-450 ¹	1
	Faldaprevir ¹	1
NS5A inhibitors	Daclatasvir	1, 3
	Ombitasvir	1, 4
	Ledipasvir	1, 4, 5, 6
	Elbasvir	1, 4
	Velpatasvir ¹	4
NS5B inhibitors		
Nucleotide-analogue	Sofosbuvir	1, 2, 3, 4, 5, 6
Non-nucleoside analogue	Dasabuvir	1
	Beclabuvir ¹	1

¹Non-FDA approved drugs.

impairment^[52,60]. In this group, the combination of grazoprevir and elbasvir appears to result in high SVR rates in the short-term^[72]. Most of the DAAs have drug-to-drug interactions, requiring the substitution or suspension of some medications during HCV treatment^[9]. The development of viral drug-induced resistance may compromise actual and future treatment options. Finally, some DAA regimens have significant cost barriers and are not fully available worldwide^[52,73].

DAAs are currently too expensive for governments worldwide, especially in some low- and middle-income countries. Nevertheless, price decreases have already been announced for some of these drugs. As patents expire, high drug costs will be reduced, although this process will take several decades. This prospect offers some hope that universal access to the treatment might be possible and that DAAs will be optimally used to reduce HCV-related mortality and incidence in low- and middle-income countries^[74,75].

ANTIVIRAL RESEARCH

Despite the progress of current DAAs in terms of SVR and treatment tolerability, difficult to treat populations and the emergence of resistant virus species indicate the continued need for research into new treatment options.

Some studies indicate that caffeine has the potential to improve liver function in patients chronically infected with HCV. Through *in vitro* research, it was possible to verify that caffeine may be an important new agent for anti-HCV therapies due to its efficient inhibition of HCV replication at non-toxic concentrations^[76].

Many researchers use the bovine viral diarrhea virus (BVDV), another *Flavivirus* member, as a surrogate model in HCV studies because propagation *in vitro* is difficult, and HCV and BVDV share similari-

ties with respect to replication cycle, biology, and genetic organization^[77]. Many studies have sought new compounds with antiviral activity from natural products. For example, a study performed in Brazil^[78] investigated the antiviral activity of several marine invertebrates and the microorganisms isolated from them. This study showed that an extract produced from the *Bacillus* genus, isolated from the sponge *Petromica citrina*, has potential antiviral activity and demonstrated an inhibition of 98% and a high selectivity index during viral adsorption. Another study performed in Brazil^[79] described the antiviral activity, with 99% of inhibition and a selectivity index greater than 200 $\mu\text{mol/L}$, of compounds produced from *Streptomyces chartreusis*, a termite-associated bacterium.

Extracts from plants have also been investigated as potential producers of novel compounds that could be used to treat HCV. For example, one study^[80] that screened Brazilian plant species described four compounds—a natural alkaloid isolated from *Maytenus ilicifolia* and three other compounds from *Peperomia blanda*—that could drastically reduce RNA levels and viral protein levels during HCV replication.

In addition to the importance of screening, and due to the number of extracts that could be evaluated, others research studies have already identified molecules from natural sources belonging to different chemical families that have antiviral activity that affects different stages of the HCV life cycle^[81]. Some active molecules cited in this review^[81] include naringenin, extracted from grapefruit, quercetin, extracted from *Embelia ribes*, honokiol, extracted from *Magnolia grandiflora*; and others.

The polyphenols excoecariphenol D and corilagin, both isolated from the Chinese mangrove plant (*Excoecaria agallocha*), were shown to potentially inhibit HCV RNA replication in cells^[82]. The monoterpene camphor, isolated from *Ocimum basilicum*, was identified as a potential virucidal, suggesting that the mechanism of action of this compound acts directly on the viral particle^[83].

Another compound known as silymarin, a flavonoid extract from the milk thistle of *Silybum marianum*, showed promising antiviral activity, both *in vitro* and *in vivo* at different stages of HCV replication: entry of the HCV into the cell hosts, RNA and protein expression and in the secretion of infectious viral particles^[84]. This compound has also been reported^[85] to potently reduce HCV RNA levels *in vivo* when administered intravenously, and to dose-dependently inhibit the HCV 3a core gene^[86].

CONCLUSION

In recent years, treatment for hepatitis C has made considerable advances, represented by an increase in SVR rates, reduction of treatment duration and reduction of AEs. However, despite these advances, the

Table 2 Treatments for hepatitis C virus infection

Ref.	Treatment, wk	Genotype	SVR (total, cirrhotic, non-cirrhotic)	Previously treated Patients included
Davis <i>et al</i> ^[53]	IFN, 24	1	3; NA; NA	Yes
	IFN + RBV, 24		30; NA; NA	
IDEAL Study Team ^[54]	PEG-IFN/RBV, 48	1	39.8-40.9; 42.1-43.6; 20.7-23.6	No
ADVANCE Study Team ^[48]	TVR + PEG-IFN/RBV	1	75; 62-81; 62	No
REALIZE Study Team ^[49]	TVR + PEG-IFN/RBV, 48	1	63-64; 28-84; NA	Yes
SPRINT-2 Investigators ^[47]	BOC + PEG-IFN/RBV, 28	1	67; 70; 50	No
	BOC + PEG-IFN/RBV, 48		68; 70; 50	
RESPOND-2 Investigators ^[46]	BOC + PEG-IFN/RBV, 36	1	59; 35; 64	Yes
	BOC + PEG-IFN/RBV, 48		66; 77; 66	
PILLAR ^[55]	SMP + PEG-IFN/RBV, 12	1	80.5; NA; 80.5	No
	SMP + PEG-IFN/RBV, 24		86.1; NA; 86.1	
Gane <i>et al</i> ^[56]	SOF + RBV, 12	2 or 3	100; NA; 100	No
	SOF + PEG-IFN/RBV, 8		100; NA; 100	
COSMOS ^[57]	SMP + SOF + RBV, 24	1	NA; 93; 79	Yes
	SMP + SOF, 24		NA; 93; 100	
	SMP + SOF + RBV, 12		NA; 93; 93	
	SMP + SOF, 12		NA; 90; 94	
OPTIMIST-1 ^[58]	SMP + SOF, 8	1	83; NA; 83	Yes
	SMP + SOF, 12		97; NA; 97	
OPTIMIST-2 ^[59]	SMP + SOF, 12	1	83; 83; NA	Yes
AI444040 Study group ^[60]	DCV + SOF, 24	2 or 3	100; NA; NA	No
	DCV + SOF + RBV, 24		86; NA; NA	No
	DCV + SOF, 24	1	100; NA; NA	Yes
	DCV + SOF + RBV, 24		95-100; NA; NA	
ALLY-3 Study Team ^[61]	DCV + SOF, 12	3	86-91; 63; 96	Yes
ION-2 Investigators ^[62]	LDV + SOF, 12	1	94; 86; 97	Yes
	LDV + SOF, 24		99; 100; 99	
	LDV + SOF + RBV, 12		96; 87; 100	
	LDV + SOF + RBV, 24		99; 100; 99	
ION-3 Investigators ^[63]	LDV + SOF, 8	1	94; NA; 94	No
	LDV + SOF + RBV, 8		93; NA; 93	
	LDV + SOF, 12		95; NA; 95	
MALACHITE- I / II ^[64]	OBV + PTV/r + DSV + RBV, 12	1	97-99; NA; 97-99	Yes
PEARL- I ^[65]	OBV + PTV/r	4	91; NA; 91	No
	OBV + PTV/r + RBV		100; NA; 100	Yes
SAPPHIRE- II ^[66]	ABT-450/r + OBV + DSV + RBV, 12	1	96.3; NA; 93.6	Yes
TURQUOISE- II ^[67]	ABT-450/r + OBV + DSV + RBV, 12	1	91.8; 91.8; NA	Yes
	ABT-450/r + OBV + DSV + RBV, 24		95.9; 95.9; NA	
ASTRAL-2 and ASTRAL-3 ^[68]	SOF + VEL, 12	2	99; 100; 99	Yes
		3	95; 93; 98	
C-WORTHY ^[69]	GZR + EBR, 12	1	91-97; 91-97; NA	Yes
	GZR + EBR + RBV, 12		90-94; 90-94; NA	
	GZR + EBR, 18		94-97; NA; NA	
	GZR + EBR + RBV, 18		97-100; NA; NA	
Everson <i>et al</i> ^[70]	DCV + ASV + BCV, 12	1	88.8-89.5; 71.4-100; 87.5-91.1	No
	DCV + ASV + BCV + RBV, 12		85.7; 100; 85	
SOUND-2 ^[71]	FDV + deleobuvir + RBV, 16	1	59; NA; NA	No
	FDV + deleobuvir + RBV, 28		59-69; NA; NA	
	FDV + deleobuvir + RBV, 40		52; NA; NA	
	FDV + deleobuvir, 28		39; NA; NA	

SVR: Sustained virological response; IFN: Interferon alfa; RBV: Ribavirin; PEG-IFN: Peginterferon alfa; TPV: Telaprevir; BOC: Boceprevir; SMP: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir; LDV: Ledipasvir; OBV: Ombitasvir; PTV/r: Paritaprevir/ritonavir; DSV: Dasabuvir; VEL: Veltapasvir; GZR: Grazoprevir; EBR: Elbasvir; ASV: Asunaprevir; BCV: Beclabuvir; FDV: Faldaprevir.

limitations of available treatments must be addressed. The difficult to treat populations and the emergence of resistant virus species indicate the continued need for research into new treatment options. Therefore, research must continue so that new substances with potential antiviral activity against this virus are identified and the limitations of existing treatments can be overcome. In addition to treatment, we must always consider the importance of prevention and the

need for global pacts that will allow these treatments to be made available throughout the world.

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