



2016 Hepatitis C Virus: Global view

Chronic hepatitis C: This and the new era of treatment

Gaetano Bertino, Annalisa Ardiri, Maria Proiti, Giuseppe Rigano, Evelise Frazzetto, Shirin Demma, Maria Irene Ruggeri, Laura Scuderi, Giulia Malaguarnera, Nicoletta Bertino, Venerando Rapisarda, Isidoro Di Carlo, Adriana Toro, Federico Salomone, Mariano Malaguarnera, Emanuele Bertino, Michele Malaguarnera

Gaetano Bertino, Annalisa Ardiri, Maria Proiti, Giuseppe Rigano, Evelise Frazzetto, Shirin Demma, Laura Scuderi, Hepatology Unit - Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy

Maria Irene Ruggeri, Internal Medicine Unit, ARNAS Civic Hospital, 90142 Palermo, Italy

Giulia Malaguarnera, Mariano Malaguarnera, Michele Malaguarnera, Research Centre "La Grande Senesce", University of Catania, 95100 Catania, Italy

Giulia Malaguarnera, Michele Malaguarnera, Department of Biomedical Sciences, University of Catania, 95100 Catania, Italy

Nicoletta Bertino, Emanuele Bertino, Faculty of Pharmacy, University of Catania, 95123 Catania, Italy

Venerando Rapisarda, Occupational Medicine Unit, Department of Clinical and Experimental Medicine, University of Catania, 95100 Catania, Italy

Isidoro Di Carlo, Adriana Toro, Department of Surgical Sciences, Organ Transplantation and Advanced Technologies, University of Catania, 95100 Catania, Italy

Federico Salomone, Gastroenterology Unit, Acireale Hospital, 95024 Acireale, Catania, Italy

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Correspondence to: Gaetano Bertino, Professor, Hepatology Unit - Department of Clinical and Experimental Medicine, University of Catania, Policlinic - Via S. Sofia n. 78, 95123 Catania, Italy. gaetanobertinounict@libero.it
Telephone: +39-09-53781573
Fax: +39-09-53781572

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Abstract

Over the last years it has started a real revolution in the treatment of chronic hepatitis C. This occurred for the availability of direct-acting antiviral agents that allow to reach sustained virologic response in approximately 90% of cases. In the near future further progress will be achieved with the use of pan-genotypic drugs with high efficacy but without side effects.

Key words: Direct-acting antiviral agents; Nucleoside inhibitors; Boceprevir; Sofosbuvir; Telaprevir; Hepatitis C; Simeprevir; Daclatasvir; Ledipasvir; Faldaprevir; Ritonavir; Ombitasvir; Dasabuvir

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Core tip: This review analyzes the current therapies for chronic hepatitis C and the future challenges of the research. So it tries to give an update on the research of hepatitis C virus (HCV) infection, providing a critical view of the emerging therapies and their impact on the future management of HCV infection. Since novel

treatments for HCV infection are highly efficacious but costly, priority should be given to patients with advanced hepatic fibrosis, which is a disease that cannot be deferred.

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INTRODUCTION

The hepatitis C virus (HCV), identified in the 70s but cloned in 1989, is a single-stranded RNA virus belonging to the family *Flaviviridae*.

HCV is the main cause of progressive liver diseases and a public health problem worldwide. It is estimated that approximately 150-180 million people in the world are living with chronic hepatitis^[1,2], 350 million of whom die each year from liver damage associated with the infection^[3].

About 80% of people infected with HCV develop chronic hepatitis, of which 20%-40% will develop liver cirrhosis or hepatocellular carcinoma (HCC) 20-30 years after infection.

As a consequence, chronic HCV infection is the major reason of liver transplantation in developed countries^[4-7].

According to the Global Burden Disease Study in Europe, the death rate for viral hepatitis is significantly higher than that for human immunodeficiency virus (HIV) and acquired immune deficiency syndrome; in particular in 2010, the number of deaths from viral hepatitis have been ten times bigger than that attributed to HIV. It is reasonable to think that this difference is due to the lack of effective therapies for HCV until a few years ago^[8].

HCV is also one of the main causes of death^[9]. The virus causes both liver damage and extra-hepatic manifestations, many of these syndromes are associated with the ability of HCV to replicate in peripheral blood mononuclear cells (PBMCs); an example is the mixed cryoglobulinemia, which is by far the most common extrahepatic disease closely connected with the infection.

Recently it was shown that antiviral treatment is associated with improved renal and cardiovascular outcomes in patients with cryoglobulinemia^[4,6,10,11]. Newly approved oral anti-HCV drugs are very safe and effective, but unfortunately their cost will force to choose a priority of treatment. The intent should therefore be to identify and treat patients with a higher risk of morbidity and mortality due to HCV.

The availability of these new oral treatments can definitely heal patients and consequently it will cause a significant reduction in health care costs^[2]. The aim of

this review article is to give an update on the research of HCV infection, providing a critical view of the emerging therapies and their impact on the future management of HCV infection.

Natural history of chronic hepatitis C

The natural history of chronic hepatitis C is partly defined. The primary HCV infection is completely asymptomatic in 60%-70% of cases, but in 80% of patients the infection becomes chronic and is characterized by the persistence of the viral genome in the blood for at least 6 mo from the onset of acute infection. In a variable proportion of people carrying the virus, especially in the presence of strong necro-inflammation and/or co-factors of liver damage, the disease can evolve from the condition of chronic hepatitis to cirrhosis and HCC.

There are several factors that can change the course, severity and progression of the disease, including age at the time of infection, route of infection, viral load, co-infection with other hepatitis viruses or HIV, alterations of immune status, and the coexistence of other hepatotoxic factors such as consumption of alcohol, iron overload, obesity, type 2 diabetes, resistance to insulin and genetic factors^[12-14].

Chronic HCV infection in about 20% of cases progresses up to hepatic cirrhosis, end-stage liver disease and HCC, generally after 20-30 years from primary infection.

The progression of chronic disease leads, through a mechanism of chronic damage, to the loss of organ function, for progressive deposition of fibrotic tissue and disruption of the parenchymal structure, and results in liver fibrosis and cirrhosis.

Cirrhosis changes the normal liver architecture, and furthermore itself represents the most important risk factor for the development of HCC, in part by acting as a cofactor accelerating the process triggered by a primary carcinogen (HCV), and specially by increased hepatocyte regeneration. Once HCV infection progresses to cirrhosis, there is a 1%-5% annual risk of HCC^[12].

The probability that a patient with compensated cirrhosis can evolve towards the decompensated form increases progressively over time.

Liver cirrhosis and its complications (portal hypertension and therefore esophageal varices, splenomegaly, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepato-pulmonary syndrome and HCC) are burdened with high morbidity and mortality.

It is also known that different variables influence the progression of the disease, for which the prognosis changes individually and is very hard to define^[12-14].

Several studies have concluded that the eradication of HCV infection slows the progression of the disease, improves the survival, and reduces the incidence of liver failure and the risk of developing liver cancer^[12-28]. The understanding of the natural history of chronic hepatitis C and its long-term consequences is essential to enable appropriate decisions on treatment, but unfortunately

the natural history of HCV infection is still the subject of much controversy. In fact, according to some authors the disease is relentlessly progressive, with a high probability to evolve to cirrhosis and HCC, while according to others the course is variable, and most patients die as a consequence of co-morbidities, not the infection itself.

Because the infection has a significant role in causing chronic hepatitis, cirrhosis and HCC, the goal of treatment is to cure HCV infection, and consequently to prevent its complications.

Although the viral RNA genome does not integrate into the host genome, the infection becomes persistent in the majority of patients, and about 70%-90% of the infected people fail to clear the virus once acquired.

It is widely known that the antiviral treatment and the achievement of a sustained virological response (SVR - defined as an absence of detectable HCV-RNA 12 mo after therapy is complete) are associated with regression of fibrosis and clinical improvement. However, despite treatment, HCV may persist in liver tissue and extrahepatic locations like PBMCs, leading to late relapse, defined as reappearance of viremia after SVR has been achieved^[29,30].

Treatment and SVR - what is the real purpose of antiviral therapy?

As mentioned above the primary goal of HCV therapy is the complete eradication of the virus, which is the SVR.

SVR was traditionally defined as HCV-RNA undetectable in serum for at least 24 wk after the end of treatment (SVR24); however, recent data suggest that the assessment at 12 wk after treatment (SVR12) is sufficient for defining this result.

Follow-up studies document that more than 99% of patients who achieve an SVR remain HCV-RNA negative 4-5 years after the end of treatment, and no signs of hepatitis have been documented.

SVR represents the main goal of antiviral therapy, indeed once achieved, the SVR is considered effective in the long term because late recurrences are rare; the SVR is associated with long-term health benefits, including improved quality of life.

SVR reduces risk for progression to cirrhosis, HCC, liver transplantation and liver-related mortality, and also decreases extra-hepatic manifestations of HCV infection (for example, cryoglobulinemic vasculitis).

Moreover it seems reasonable to assume that a lasting biochemical and virological response induced by treatment can also lead to improved liver fibrosis^[31-39].

For decades the antiviral therapy of chronic HCV infection was based on the administration of interferon (IFN), initially as monotherapy and subsequently in combination with ribavirin (RBV). Dual therapy with "pegylated IFN (PEG-IFN) and RBV" achieves SVR rates of 40% to 50% in patients with genotype 1, and about 80% in those with genotypes 2, 3, 5 and 6; the results for genotype 4 are intermediates.

In 2011, the first direct-acting antivirals boceprevir

and telaprevir have been approved in combination with PEG-IFN and RBV. These drugs are protease inhibitors (PIs) and increase SVR rates in both naive patients and in experienced patients, compared to dual therapy^[40-46]; however, they were dropped due to their significant toxicity.

With the advent of new oral antiviral regimens, with better efficacy and tolerability, and a shorter treatment duration, the number of patients that can be treated is expected to increase significantly, and also the SVR rates will improve to approximately 95% or plus^[47].

HCV and host: The HCV replication cycle and mechanisms of action of the new direct acting antiviral agents

HCV is classified within the *Flaviviridae* family, as the only member of a distinct genus called *Hepacivirus*^[48].

The lack of detailed information on the viral replication cycle has significantly prevented the development of direct acting antivirals.

For decades the antiviral therapy of chronic HCV infection was based on the administration of IFN, initially alone and then in combination with RBV, but this regimen was effective in only 50% of patients with genotype 1, with significant side effects^[49-54].

In the last decade the development of *in vitro* models of viral replication has thus represented a turning point for the understanding of the different stages of the replication cycle, and quickly has led to the design and introduction of direct acting antivirals (DAAs)^[55].

However, because of huge variability of the virus, new drugs cannot be administered as monotherapy because it would quickly lead to the selection of drug-resistant viral variants.

HCV indeed is characterized by an extremely high degree of variability. The genetic heterogeneity of HCV gives an adaptive advantage as the simultaneous presence of multiple genomic variants allows rapid selection of mutants that better adapt to environmental changes (for example resistance to drugs or the immune response); this genetic heterogeneity is the basis of chronic infection, and is probably involved in the phenomena of evasion of the immune response and in the limited efficacy of treatment^[56-59].

The HCV replication cycle occurs in the cytoplasm, and can be summarized as follows: (1) entry into the host cell and release of viral genomic RNA into the cytoplasm; (2) translation of RNA, processing of the viral polyprotein and formation of a replication complex associated with intracellular membrane; (3) using positive RNA for the synthesis of an intermediate negative RNA for the production of new positive RNA molecules with different destination; and (4) release of viral progeny into circulation from infected cells. The infectious viral structure is comprised of envelope glycoproteins in a lipid bilayer, that contain the viral core protein and RNA^[60-63].

After cell entry, the viral RNA is translated through the host machinery into a polyprotein, which is cleaved

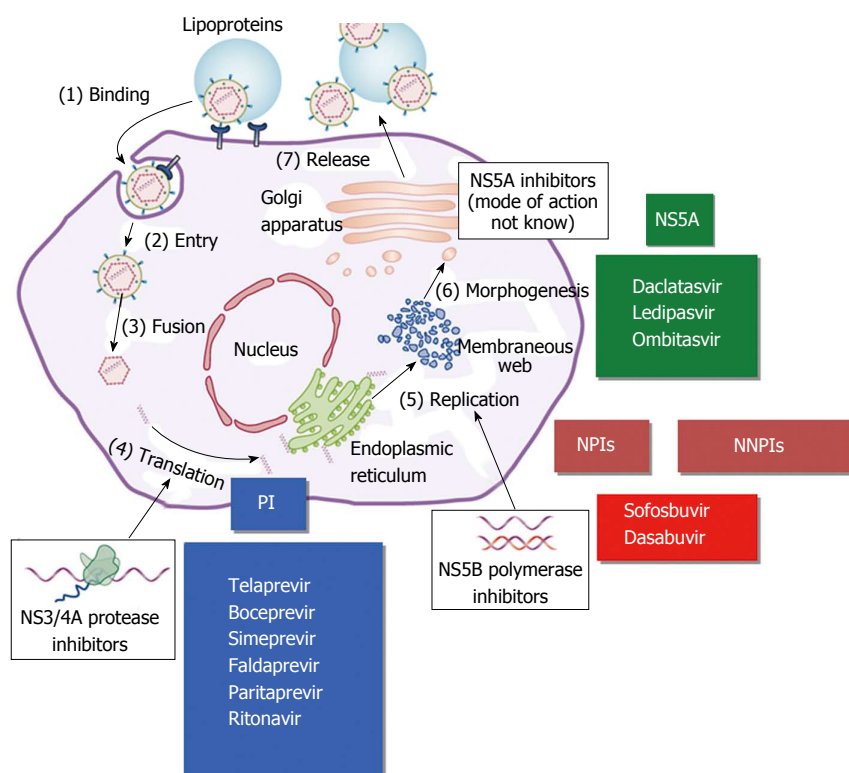


Figure 1 Hepatitis C virus replicative cycle and main targets for direct acting antiviral agents. Modified from Manns and Cornberg. *Lancet Infectious Diseases* 2013. PIs: Protease inhibitors; NPIs: Nucleoside polymerase inhibitors; NNPIs: Non-nucleoside polymerase inhibitors.

during and after translation by both host and viral-encoded proteases into 10 mature viral proteins, including several non-structural (NS) proteins. One of the viral proteases involved in this post-translational processing is a heterodimeric complex of the NS3 and NS4A proteins (NS3/NS4A). NS3 has the proteolytic activity and NS4A is a membrane protein that acts as a cofactor. Synthesis of new viral RNA occurs in a highly structured replication complex that consists of NS3, NS4A, NS4B, NS5A, and NS5B. NS5B is an RNA-dependent RNA polymerase that is essential for viral replication. NS5A has a presumptive role in the organization of the replication complex and in regulating replication. It is also involved in assembly of the viral particle that is released from the host cell (Figure 1)^[64-69].

Therapies

Increased knowledge of the HCV replication cycle and genomic diversity has driven the development of antiviral agents specifically targeting well-conserved proteins required for efficient viral replication. Aside from PEG-IFN, HCV-specific therapeutic agents that have gained widespread use or reached late-stage clinical trials include NS3 PIs, nucleoside and nucleotide analogues, and other NS5B polymerase inhibitors.

DAAs

After year of IFN-based therapy, the introduction of DAAs has increased the number of patients who respond to treatment, and has changed radically the treatment of chronic HCV genotype-1 infection^[43,70-72].

Thanks to the discovery of key viral replication targets such as the NS3/4A protease, NS5A, and the NS5B RNA polymerase, other potent antiviral inhibitors were licensed in 2014.

These new regimens include the addition of simeprevir (SMV) (a second-generation PI), daclatasvir (an NS5A inhibitor), and sofosbuvir (an uridine nucleotide prodrug NS5B polymerase inhibitor), in combination with PEG-IFN and RBV for 12-24 wk^[73,74].

The main targets of the DAAs are the HCV-encoded proteins that are vital to the viral replication. The DAAs have a high barrier to resistance and ideally, they should also be active against all HCV genotypes. Furthermore, these drugs are well tolerated and have few drug interactions.

There are four classes of DAAs, which are defined by their mechanism of action and therapeutic target^[75] (Figure 2 and Table 1): (1) NS3/4A PIs; (2) NS5B nucleoside polymerase inhibitors (NPIs); (3) NS5B non-NPIs (NNPIs); and (4) NS5A inhibitors.

NS3/4A PIS

NS3/4A PIs are drugs that inhibit the NS3/4A serine protease, an enzyme involved in post-translational processing and replication of HCV^[76].

There are two generation of PIs.

First-generation PIs (telaprevir and boceprevir)

The first-generation PIs telaprevir and boceprevir were the first DAAs available for the treatment of CHC^[77].

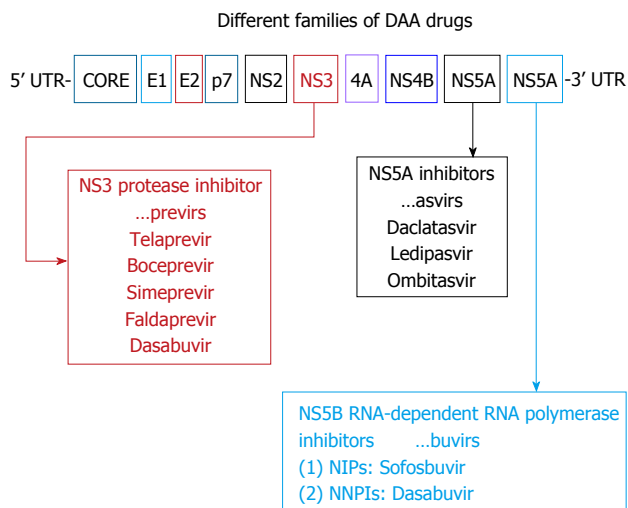


Figure 2 Direct acting antiviral agents. Modified from Alexopoulou *et al.*^[121]. Interferon-based combination treatment for chronic hepatitis C in the era of direct acting antivirals. *Annals of Gastroenterology* 2015; 28: 55-65. NPIs: Nucleoside polymerase inhibitors; NNPIs: Non-nucleoside polymerase inhibitors; DAA: Direct acting antiviral.

The addition of PIs to PEG-IFN and RBV has become the new standard of care for the treatment of genotype 1 infection, and so, in 2011, has increased the efficacy of PEG-IFN and RBV in patients with chronic HCV genotype 1 infection.

Telaprevir and boceprevir were approved for the treatment of chronic HCV genotype 1 infection by the Food and Drug Administration (FDA) and European Medicines Agency in combination with PEG-IFN- α and RBV in adults with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous IFN and RBV therapy^[78].

Telaprevir and boceprevir are NS3/4A PIs, and they both have the same molecular target: The HCV NS3/4A serine protease.

They have an high antiviral potency only against genotypes 1 and 2, but a low barrier to resistance^[79].

Monotherapy with these agents resulted in the selection of drug resistant variants, so they should always be used in triple combinations together with PEG-IFN and RBV in a triple therapy regimen to reduce the frequencies of resistant mutants and viral breakthrough, and they can improve the SVR rates by 15% to 20% compared with PEG-IFN- α and RBV^[42,43,80].

Viral resistance may develop even in triple combinations with PEG-IFN and RBV, and due to this problem strict stopping rules are applied in triple therapy-based regimens.

Response to HCV therapy in genotype 1 can be predicted by identifying the single nucleotide polymorphisms located in the region of interleukin-28B (*IL-28B*) gene through genome-wide association studies.

High response rates have been reported in patients with CC genotype of *IL-28B* as compared to CT or TT *IL-28B*-genotype (70% vs 25%-30%). Testing for *IL-28B* genotype is thus a useful tool in the management

NS3/4A PIs	First-generation protease inhibitors Telaprevir Boceprevir
	Second-generation protease inhibitors Simeprevir Faldaprevir Paritaprevir Ritonavir
NS5B NPIs	Sofosbuvir
NS5B NNPIs	Dasabuvir
NS5A inhibitors	Daclatasvir Ledipasvir Ombitasvir

PIs: Protease inhibitors; NPIs: Nucleoside polymerase inhibitors; NNPIs: Non-nucleoside polymerase inhibitors.

of patients^[81].

First-generation PIs increase the number of patients with genotype 1 infection who respond to treatment, however, the side effect profiles of these triple combination therapies are not favourable, because it can cause clinically significant adverse events.

The most common side effects of telaprevir are anaemia, pruritis, nausea, diarrhoea, and anorectal discomfort. Around 4% of patients develop severe dermatitis, necessitating cessation of treatment.

Drug reactions like eosinophilia and systemic symptoms or Stevens-Johnson syndrome are rare, but have been reported. Boceprevir causes dysguesia and anaemia^[43].

Several drug-drug interactions can occur, so the use of first-generation PIs has been significantly restricted^[82].

Second-generation PIs

Second-generation PIs offer several benefits, for example, few drug-drug interactions and less frequent and less severe side effects.

In addition, second-generation PIs also appear to have increased efficacy against genotype 1 HCV^[83]; as treatment options have progressed and improved, HCV- 1, HCV-2 and HCV-4 are considered to be easy to treat^[84] but HCV genotype 3 infection has become the most difficult to treat.

SMV: SMV was the first available second-generation PI with antiviral activity against genotypes 1, 2, 4, 5 and 6^[85].

SMV is administered orally as a daily pill, and has limited drug-drug interactions.

No dose recommendation can be given for patients with Child-Pugh class B or C cirrhosis, because higher SMV exposure (particularly in Child-Pugh C patients) may be associated with increased frequency of adverse reactions. No dose adjustment is required in the setting of renal impairment, because SMV is eliminated by the liver^[85]. SMV is well tolerated, and adverse reactions in patients receiving SMV in combination with PEG-IFN- α

and RBV are rash, pruritus and nausea. Because SMV is an inhibitor of the transporters OATP1B1 and MRP2, mild, transient hyperbilirubinaemia not accompanied by changes in other liver parameters was observed in approximately 10% of cases. SMV is oxidatively metabolized by CYP3A subfamily, which consists mainly of hepatic and intestinal CYP3A4 metabolism^[86]. Co-administration of SMV with inhibitors of cytochrome P450 3A (CYP3A) is not recommended.

In post-liver transplant patients with HCV infection, co-administration of SMV with cyclosporine resulted in significantly elevated SMV levels, so it is not recommended^[87]. SMV can be safely administered with tacrolimus or sirolimus. SMV was approved by the FDA for genotype 1 treatment in November 2013 under the name of "OLYSIO", in Japan it was licensed in September 2013, finally in Europe in May 2014 (European Medical Agency approval).

In phase II of COSMOS trial, sofosbuvir (SOF; 400 mg daily) was administered in combination with SMV (SMV 150 mg daily) with or without RBV for 12 wk or 24 wk in genotype 1 patients. SVR12 rates were not different between 12 or 24 wk of treatment, with or without RBV, and comparing naive patients to experienced (95% vs 91%)^[87,88].

In this small study, the regimen SOF plus SMV with or without RBV was well tolerated; the most common side effects were headache, fatigue, and nausea, and only four (2%) patients discontinued treatment due to these events.

Although the results of this study are encouraging, due to the small number of patients and the future availability of other oral regimens with better antiviral efficacy and fewer side effects, this regimen should be considered as a second-line option.

Two phase III trials of SMV/SOF without RBV are ongoing (OPTIMIST-1 and -2)^[89]. These studies provide us much bigger data about SOF/SIM regimen, and investigate the efficacy and safety of SMV 150 mg in combination with sofosbuvir 400 mg in HCV genotype 1 infected naïve or experienced patients, with and without cirrhosis.

SMV/SOF treatment led to high SVR12 rates in patients infected with HCV GT-1 subtype, regardless of treatment duration or the addition of RBV. SVR12 rates were high, regardless of baseline characteristics, including HCV GT-1 subtype, *IL-28B* allele, or Q80K polymorphism. On-treatment virologic response, including RVR, was not predictive of SVR. Two ongoing phase III trials are investigating SMV/SOF without RBV (OPTIMIST-1 and -2).

Baseline predictive factors significantly associated with virologic relapse were male sex, body weight \geq 75 kg, *IL-28B* non-CC allele, cirrhosis, baseline HCV RNA \geq 800000 IU/mL, and prior treatment failure. Current SOF regimens are highly efficacious, even in patients with multiple traditional negative predictors of diminished efficacy; SVR12 rates are comparatively lower in patients who have five or six negative predictors^[90,91].

The approval of the treatment scheme "SMV plus PEG-IFN/RBV" is based on a clinical trial program comprising three phase III studies, with more than 1000 patients with genotype 1.

The studies, QUEST-1, QUEST-2 and PROMISE, have evaluated the use of SMV in combination with PEG-IFN/RBV in naive patients (Quest-1 and 2)^[92,93] and relapsed patients (PROMISE^[94]) after an IFN-based treatment. All three studies have shown that SMV, in combination with PEG-IFN/RBV, gets significant SVR rates when compared to PEG-IFN/RBV.

A triple therapy with SMV, PEG-IFN and RBV has been recommended for genotype 1 also after the data of other four phase III trials: CONCERTO-1, -2, -3 and -4^[95-98].

Faldaprevir: Faldaprevir is one of the new-generation NS3/4A PIs in development. It is a pan-genotypic potent NS3/NS4 PI (antiviral activity against genotypes 1, 2, 4, 5 and 6 *in vitro*). It was used in genotype 1 infection in two combinations: (1) a triple regimen with faldaprevir, PEG-IFN and RBV for a total of 24 wk^[98,99]; and (2) IFN-free regimens with faldaprevir and deleobuvir with or without RBV^[100,101].

In both combinations faldaprevir provides high SVR rates, but IFN-containing regimens registered most cases of breakthrough and relapse, while with the IFN-free combination of faldaprevir and deleobuvir with RBV, very encouraging results were obtained^[102].

Faldaprevir is administered orally, once a day. The most common adverse events are gastrointestinal dysfunction, rash and photosensitivity skin. Faldaprevir in combination with PEG-IFN and RBV appears to be associated with fewer adverse events than the first PIs telaprevir and boceprevir.

Paritaprevir and ritonavir: Paritaprevir is an HCV protease inhibitor that is given with low dose ritonavir for a pharmacologic boosting effect.

Ritonavir is a protease inhibitor that does not have anti-HCV activity but it is a pharmacoenhancer that is included to increase levels of paritaprevir through inhibition of CYP3A-mediated metabolism

Paritaprevir and ritonavir are available as a fixed-dose combination with ombitasvir and given with the non-nucleoside NS5B inhibitor dasabuvir. This regimen is given with and without RBV for the treatment of HCV GT-1 subtype^[103].

NS5A INHIBITORS

The NS5A is a multifunctional non-structural protein involved both in viral replication and in the assembly of HCV^[104]. However, the precise molecular mechanisms of HCV NS5A inhibitors are unclear.

NS5A inhibitors have high antiviral activity against a lot of genotypes, but a low genetic barrier. They significantly reduce HCV-RNA levels and enhance SVR when given in conjunction with PEG-IFN and RBV. They

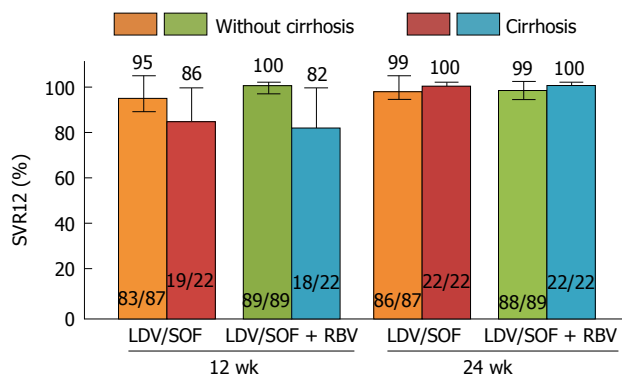


Figure 3 ION-2 sub-analysis of cirrhosis vs without cirrhosis. Error bars represent 95% CIs. LDV: Ledipasvir; RBV: Ribavirin; SOF: Sofosbuvir; SVR12: Sustained virologic response at 12 wk post-treatment.

also result in very high SVR rates among patients with genotype 1 infection when given in combination with other direct-acting antivirals with or without RBV^[105].

Daclatasvir

Daclatasvir is a pangenotypic NS5A inhibitor that is available for use in Europe. According to EASL guidelines daclatasvir should be administered orally (60 mg once daily) with low potential for drug-drug interactions. It is well tolerated. Dose adjustments are not needed in patients with Child B or C disease. Side effects with daclatasvir are fatigue, headache, and nausea. Little information has been released on daclatasvir drug-drug interactions.

In previously untreated patients infected with genotype 2 or 3, SVR was reported in 94%-100% of patients treated with the combination of daclatasvir plus sofosbuvir. In the ALLY-3 study^[106], 133 patients with genotype 3 infection were treated for 12 wk with 400 mg of sofosbuvir and 60 mg of daclatasvir for 12 wk. Ninety-one percent of previously untreated patients had an SVR compared with 86% of treatment-experienced patients.

In the COMMAND GT2/3 study, Dore *et al.*^[107] compared the efficacy and safety of daclatasvir plus PEG-IFN- α -2a/RBV administered for either 12 or 16 wk with a standard 24-wk course of PEG-IFN- α -2a/RBV in HCV GT-2 or GT-3 subtype. Daclatasvir has been given with PEG-IFN- α -2a/RBV for 12 or 16 wk to previously untreated patients with genotype 2 or 3 infection. Around 83% of patients infected with genotype 2 and 70% of patients with genotype 3 infection have been reported to achieve SVR^[107]. In another open-label study, the drug's effectiveness has been demonstrated^[108].

Other NS5A inhibitors

Other NS5A inhibitors available in the United States are ledipasvir and ombitasvir, and they are each available in fixed-dose combinations with other direct-acting antivirals.

Ledipasvir: Ledipasvir is the first NS5A inhibitor

available in the United States. Ledipasvir and sofosbuvir are co-formulated in a single tablet in a fixed-dose combination (90 mg ledipasvir/400 mg sofosbuvir) that is administered once daily with or without food. This combination is well tolerated, and ledipasvir has the same drug interactions as sofosbuvir. This regimen is administered with or without RBV, depending on the patient population, in genotype 1 infection.

Ombitasvir: Ombitasvir (also known as ABT-267) is available as a fixed-dose combination with the PIs paritaprevir and ritonavir (12.5 mg ombitasvir/75 mg paritaprevir/50 mg ritonavir). This single tablet is administered orally with an additional drug: The non-nucleoside polymerase (NS5B) inhibitor dasabuvir^[109,110]. This regimen is given with and without RBV in genotype 1 infection.

The combination ombitasvir-paritaprevir-ritonavir plus dasabuvir is generally well tolerated, and mild adverse effects are nausea, pruritus, insomnia, diarrhea, and asthenia^[111,112]. Some of these symptoms may be attributable to RBV^[113,114].

The most important studies that evaluated treatment duration of ledipasvir/sofosbuvir treatment and its safety and efficacy (SVR12) in naive and treatment-experienced patients are ION-1, LONESTAR, and ION-2^[115-117] (Figure 3).

NS5B RNA-DEPENDENT RNA POLYMERASE INHIBITORS

NS5B is an RNA-dependent RNA polymerase involved in post-translational processing that is necessary for replication of HCV. The structure of NS5B is highly conserved across all HCV genotypes, so the drugs that inhibit NS5B have efficacy against all six genotypes.

There are two classes of polymerase inhibitors: NPis and NNPIs. These two classes generally differ in specificity, according to their mode of action.

The NPis mimic natural components and thus are incorporated into the nascent RNA chain, causing premature chain termination^[118]. NNPIs act as allosteric inhibitors, and in fact they bind to one of four allosteric sites on the surface of NS5B.

NPis

NPis have high antiviral efficacy across all genotypes, although they have a very high barrier to resistance.

Sofosbuvir: Sofosbuvir is the first NS5B NPI available in the United States.

Sofosbuvir is a pangenotypic NS5B polymerase inhibitor with a high barrier to resistance and favorable clinical pharmacology profile. It is administered orally as a 400 mg pill once a day, and has no food effect. Sofosbuvir is well tolerated, and the most commonly reported side effects of sofosbuvir and RBV, with or without PEG-IFN, are fatigue, headache, nausea,

insomnia, and anemia^[74,119].

Although renal clearance is the major form of elimination, in patients with mild or moderate renal impairment (glomerular filtration rate greater than 30 mL/min)^[120], any adjustment dose is not required.

No dose adjustment has been needed in patients with moderate (Child Pugh class B) or severe (Child Pugh class C) hepatic impairment.

Sofosbuvir has substantially less drug interactions than those observed with the HCV PIs. Sofosbuvir is a substrate of P-glycoprotein (P-gp), a drug transporter, so drugs that are potent intestinal P-gp inducers may decrease sofosbuvir levels. Thus, coadministration of sofosbuvir is not recommended with rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir.

Sofosbuvir was approved by FDA for genotype 1 in combination with PR, and in genotypes 2 and 3 in IFN free regimens in December 2013, in Canada during the same month and in Europe in January 2014 (European Medical Agency approval).

In the NEUTRINO study (an open-label, single-arm phase III registration trial) 327 treatment-naïve patients were treated with a regimen comprising sofosbuvir plus PR for 12 wk^[119]. The overall patient population included mainly those infected with genotype 1 (89%) as well as a few patients infected with genotypes 4, 5 and 6; 17% of patients in this trial had cirrhosis. This sofosbuvir-based triple-therapy regimen resulted in a very high RVR, with the 4-wk RVR rate approaching 99%. The SVR rate for the entire trial population remained high at 90%, 12 wk after the end of treatment (with 99% of patients achieving virologic response at the end of treatment). Analyzing the groups based on viral genotype, patients with genotype 1 had an SVR rate of 89%, and the small number of patients with genotype 4, 5 and 6 had SVR rates between 96% and 100%. Overall, this sofosbuvir-based triple therapy regimen resulted in very high SVR rates across all genotypes that were evaluated. One important point from the NEUTRINO trial was the relative decrease in the overall response rate for patients with cirrhosis (SVR, 80%) compared with non-cirrhotics (SVR, 92%)^[121].

Other representative studies on genotype 1 are ELECTRON, QUANTUM, VALENCE and LONESTAR-2^[122-125].

Genotypes 2 and 3 have been studied together in three sofosbuvir phase III trials (FISSION, POSITRON, and FUSION)^[119,122,126].

Therapy with sofosbuvir-RBV for 12 wk in patients with HCV genotype 2 infection and for 24 wk in patients with HCV genotype 3 infection resulted in high rates of SVR^[127].

To date there are very few data on genotype 4 patients treated with sofosbuvir without PEG-IFN^[128]. There are no data currently on treatment-experienced populations or any patients with genotypes 5 and 6^[129].

Sofosbuvir is used in various combinations with other antivirals for different indications: (1) with ledipasvir for HCV GT-1; (2) with SMV (\pm RBV) for HCV GT-1;

(3) with RBV for HCV GT-2, -3, -4, -5, and -6 infection (and among patients with any genotype awaiting liver transplant); and (4) with PEG-IFN and RBV for genotypes HCV GT-1 and -4.

NNPIs

NNPIs bind to one of four allosteric sites on the surface of NS5B and cause a conformational change, making the enzyme ineffective. Despite the active site of NS5B is well conserved across all genotypes, and they should have a pan-genotype antiviral activity, NNPIs have a more limited spectrum of activity specifically targeting against GT-1 (all NNPIs in clinical development have been optimized for GT-1). They have a low to moderate barrier to resistance variable toxicity profiles^[130]. Consequently, this class of drug has been studied primarily as an adjunct to more potent compounds with higher barriers to resistance.

Dasabuvir: Dasabuvir is a non-nucleoside polymerase (NS5B) inhibitor administered with the fixed-dose combination ombitasvir-paritaprevir-ritonavir (12.5 mg ombitasvir/75 mg paritaprevir/50 mg ritonavir).

ABT-450/ritonavir with ombitasvir (ABT-267) and dasabuvir (ABT-333):

TURQUOISE- II is a global, multi-center, randomized, open-label study evaluating the efficacy and safety of 12 or 24 wk of treatment with ABT-450/ritonavir (150/100 mg) co-formulated with ombitasvir (ABT-267) 25 mg, dosed once daily, and dasabuvir (ABT-333) 250 mg with RBV in adult patients with GT-1 HCV infection with compensated liver cirrhosis. Patients achieved SVR₁₂ rates of 91.8% and 95.9% in the 12 and 24-wk treatment arms, respectively^[131]. In TURQUOISE- II, both cirrhotic non-responders and treatment-naïve cirrhotic subjects achieved higher SVR rates if they were genotype 1b-infected vs genotype 1a-infected. According to Asselah *et al.*^[132] we support the efficacy and safety profile in GT-1 HCV cirrhotic patients, and in some cases the efficacy was demonstrated also in borderline compensated cirrhosis. However, current data in patients with cirrhosis and other HCV genotypes, such as genotype 3 and 4, are clearly an unfulfilled need. Another significant study is the PEARL- II^[133].

New drugs: Cyclophilin A inhibitors

Cyclophilins (Cyp) are host proteins involved in the HCV lifecycle. CypA binds to the non-structural protein NS5A of HCV to promote replication of viral RNA, so molecules that are CypA antagonists, such as cyclosporines, are potent inhibitors of HCV replication. NS2, a non-structural protein of HCV involved in virus assembly, also plays an important role in the inhibitory effect of CypA inhibitors; NS2 modulates HCV sensitivity to cyclosporines and so NS2 may increase the inhibitory effect of cyclosporines on HCV replication^[134,135].

Alisporivir, is the first Cyp A inhibitor in clinical development. It is a cyclosporine analog without immunosuppressive properties, and due to its mechanism of

action, alisporivir is a pangenotypic antiviral, provides a high barrier for development of viral resistance, and does not permit cross-resistance to direct-acting antivirals.

This drug is also well tolerated. This drug has been used alone or in combination with PEG-IFN and RBV with very promising results^[136,137].

GUIDELINES TREATMENTS HEPATITIS C

The treatment of CHC is performed following the American, European and Italian guidelines (AASLD, EASL, and AISF guidelines); this allows to optimize the therapy and customize it for various patient characteristics. Priority should be given to patients with advanced disease, patients with extrahepatic manifestations, HIV coinfection, post-liver transplantation recurrence and non-hepatic solid organ transplant recipients. Patients with mild disease can be treated with regimens containing PEG-IFN or deferred up to a worsening of the disease and the degree of liver fibrosis^[138,139].

DISCUSSION AND CONCLUSION

Today, it can be anticipated that the future of HCV infection treatment seems very bright after the addition of first-generation HCV PIs as well as SMV and the first-in-kind HCV RNA polymerase inhibitor, "sofosbuvir", in the standard of care (*i.e.*, PEG-IFN/RBV). However, the real success of these drugs is very much dependent on careful monitoring of viral load and resistance, patterns of response to previous treatment, side effects and drug-drug interactions. Moreover, the logical meaning of novel emerging therapies must be to achieve high SVR and thorough clearance of the virus from treated patients. Nevertheless, the triple therapeutic regimens have several limitations. First, concomitant use of PEG-IFN plus RBV is essential to prevent the emergence of viral escape mutants and viral breakthrough during triple therapy. Second, triple therapy becomes less effective in prior null responders to PEG-IFN plus RBV and cannot be administered to patients who are contraindicated for PEG-IFN or RBV. To overcome these limitations, in the near future, many patients will be treated with two or more DAAs with or without IFN- α plus RBV based combination therapies. Currently, the approval of sofosbuvir- and SMV-based IFN-free regimens is an indication in this way. Triple and quadruple treatment regimens including multiple DAAs with or without PEG-IFN and RBV will likely be a suitable option for difficult-to-treat populations and for the prior null responders. All-oral IFN free regimens including drugs with a high genetic barrier to antiviral resistance (*e.g.*, NS5B inhibitors) and high antiviral efficacy (*e.g.*, NS3/4A PIs or NS5A inhibitors) may be a potent option for numerous patients contraindicated for PEG-IFN plus RBV. All oral regimens consisting of daclatasvir plus sofosbuvir once daily presented higher rates of SVR in untreated HCV GT-1, -2 and -3 infected patients and

in HCV GT-1 infected patients who had failed previous treatment with PIs. We hope that such combinational treatment strategies will become "the weapon" to treat the majority of HCV infected patients who represent the difficult population (*i.e.*, *IL-28* polymorphism, HCV genotypes 1 and 4 subtypes, receipt of RBV, and the emergence of resistant variants) and will be more efficient to access the treatment in the near future. The testing of adenovirus vector based vaccines, which escalate the innate and acquired immune response against the most conserved regions of HCV genome in chimpanzees and humans, may be a promising therapeutic approach against HCV in the near future, although its fate still needs to be exploited fully in diverse HCV populations. One thing must be of special concern is whether the newly developed or being developed DAAs added in triple or quadruple therapies are safer or not than antiretroviral and traditional IFNs. Overall, the achievements in the field of HCV medicines may predict that we are near to complete elimination of HCV disease in the world^[140]. The real challenges that our efforts must be directed are: (1) the effectiveness of IFN-free regimens in HCV-3, especially in cirrhotic non-responders; in this setting, combination with PEG-IFN is still possible; (2) the effectiveness of IFN-free regimens in decompensated cirrhosis are scarce in relation to the current correlation data between SVR and clinical outcome (literature confirms that the results of IFN-free regimens are good in compensated cirrhosis even if further clinical development is necessary in certain groups to improve SVR rates); (3) the development of new treatment strategies for patients who show resistance to new drugs; and (4) free-access to care^[141]. In fact, many patients with CHC have mild disease and are currently excluded from the interferon-free treatment. In the near future we will inevitably prioritize this category in order to prevent progression to cirrhosis, decompensation and HCC.

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P- Reviewer: Abenavoli L, Han SY, Rodriguez-Frias F, Tovo CV
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