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New Perspective in HCV Clinical and Economical Management of the Current and Future Therapies

P. Pierimarchi, G. Nicotera, G. Sferrazza, F. Andreola, A. Serafino and P.D. Siviero

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Abstract

Hepatitis C virus (HCV) is a progressive disease that infects more than 185 million individuals worldwide and is associated with persistence of viral replication and ongoing necroinflammation and fibrosis. To date 20% of patients chronically infected with HCV progress to cirrhosis. Epidemiological studies demonstrate that the incidence of HCV is not well known, because acute infection is generally asymptomatic. The global prevalence is about 2.2% and there is a large degree of geographic variability. Before the 2011, the gold standard of therapy for the treatment of chronic hepatitis C (CHC) was based on the combination of pegylated Interferon (peg-IFN) and Ribavirin (RBV). However, several aspects related to safety profile limited their use in clinical practice. In the recent years, thanks to basic research on HCV structure and replicative cycle, it has been possible to develop direct acting antiviral drugs that have dramatically increased the viral clearance rate. Specifically, the advent of the triple therapy employing direct acting antivirals has dramatically increased the viral clearance rate, from less than 10%, with the initial regimen of IFN monotherapy, to more than 95% with the current therapy. Even though new medications for hepatitis C are effective disease modifiers and have the potential, in a long term perspective, to eradicate the pathology, the cost of new treatments are unlikely to be sustainable for the NHSs. The evidence documenting the effectiveness and tolerability of the new therapies for HCV and several pharmacoeconomic analysis, shows that despite the cost, the new treatments can be considered cost-effective in the long period. However, the health care systems are unable to compensate the height financial resources immediately needed for treating patients with the long terms savings that will be obtained from the eradication of HCV. Indeed, new pharmaceutical policy and a global commitment is required to improve strategies of treatment and price negotiation with pharmaceutical companies to move from a theoretical cost-effectiveness approach to a practical cost-sustainable reality.

Keywords: HCV, Hepatitis, DAAs

1. Introduction

Hepatitis C virus (HCV) is a progressive disease that infects more than 185 million individuals worldwide and is associated with persistence of viral replication and ongoing necroinflammation and fibrosis. To date, 20% of patients chronically infected with HCV progress to cirrhosis.

Epidemiological studies demonstrate that the incidence of HCV is not well known since acute infection is generally asymptomatic. The global prevalence is about 2.2%, and there is a large degree of geographic variability. Before the 2011, the gold standard of therapy for the treatment of chronic hepatitis C (CHC) was based on the combination of pegylated interferon (peg-IFN) and ribavirin (RBV). However, several aspects related to safety profile limited their use in clinical practice. In the recent years, thanks to basic research on HCV structure and replicative cycle, it has been possible to develop direct acting antiviral drugs that have dramatically increased the viral clearance rate. This new therapeutic strategy contemplates the use of interferon-free treatment protocols that are shorter and well tolerated, and this might improve the management of patients. These new medications for hepatitis C are effective disease modifiers and could potentially eradicate the infection in a long-term perspective. However, their costs are even high and unlikely sustainable for the National Health Systems (NHSs), and new pharmaceutical policy and a global commitment are required for achieving the universal access to new treatment strategies.

2. Structure and replicative cycle of HCV

The structure of the HCV virion remains poorly characterized despite several substantial progress in biochemical and morphological studies, and most of the HCV proteins are now actively being pursued as antiviral targets. HCV, discovered in 1989, is a positive-sense, single-stranded RNA virus, approximately 9600 nt in length, which belongs to the Flaviviridae family (*Flavivirus* genus), also including many arthropod-borne human pathogens such as yellow fever virus, West Nile virus, and dengue virus. HCV has been classified by the World Health Organization (WHO) as an oncogenic virus [1]. HCV-RNA encodes a polyprotein that is cleaved by cellular and viral proteases into structural and nonstructural proteins, each with a specific function. The structural proteins include two envelope glycoproteins E1 and E2, which are targets of the host antibody response and are crucial for viral entry and fusion, and a core protein (C), which interacts with the viral genome to form the nucleocapsid. The nonstructural proteins P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B form a complex with the RNA of the virus to initiate viral replication, which occurs by budding through intracellular membranes. Mature virions are released into the extracellular milieu by exocytosis, and nascent virions incorporate cellular lipoproteins and apolipoproteins (e.g., apoE and apoB) as lipoviral particles [2]. HCV specifically infects hepatocytes, entering the cells by receptor-mediated endocytosis. During primary infection, HCV particles are transported by the blood stream and come in contact with hepatocytes after spanning the fenestrated endothelium of the liver sinusoids. In the Disse space, virions are in direct contact with the basolateral surface of hepatocytes that interact with multiple cell surface molecules, including attachment factors

and receptors. Upon cell surface attachment, the subsequent steps of HCV entry are only partially known, but a putative mechanism has been described in analogy with other Flaviviridae [3]. The virus/receptor complex is internalized, and the nucleocapsid is released into the cytoplasm, decapsidated, and the free viral RNA is used for both polyprotein translation and replication in the cytoplasm. Replication and posttranslational processing seem to take place in a membranous site constituted by viral nonstructural proteins and host cell proteins, the *replication complex*, located in close contact with the perinuclear membranes. Genome encapsidation presumably takes place in the endoplasmic reticulum, and nucleocapsids are enveloped and matured into the Golgi apparatus before the release of new virions in the extracellular space by exocytosis [4]. There are seven main known genotypes (GT) of HCV (from GT-1 to GT-7) that have been classified into 67 subtypes with distinct geographic distributions, modality of transmission, and sensitivity to interferon-based treatments [5]. Estimates of genotype distribution within 98 countries show that the most widespread genotype is the GT-1 (46%), with the subtypes 1a and 1b that are the most common in the United States and in Europe, respectively. Afterward, there are the GT-3 (22%), frequent among drug users; the GT-2 (13%), mainly present in the Mediterranean area; and the GT-4 (13%), mainly present in Egypt and other Arabic countries. GT-7 is extremely rare, and the incidence and prevalence are not yet known [5]. These seven genotypes are responsible for 97% of all infections present worldwide [6]. Although there are no differences in the risk of cirrhosis among all genotypes, GT-3 and GT-1b are associated with increased rate of hepatic steatosis and of hepatocellular carcinoma, respectively [7]. In addition, all these genotypes show different frequencies of polymorphisms associated with resistance to several classes of virus-targeting drugs [8].

3. The role of immune response in HCV infection

HCV has a very high replicative capacity, and a viral titer of $>10^6$ IU/mL can be measured in the serum within days after infection (averages 1–2 weeks) [9]. Innate immune response is the first line of host defense during infection, and interferons (IFNs) are the family of cytokines specialized in coordinating immunity against viruses and for the induction of an antiviral state in cells, by activation and regulation of cellular components of innate immunity, such as natural killer (NK) cells [10]. Furthermore, the induction of the endogenous IFN system in the liver can be ineffective in clearing the infection and in preventing response to therapies with peg-IFN and RBV [11,12]. Types I and II IFNs are in general the major elements of the innate immune response against viruses [10]. Type III IFN family (also known as IFNs- λ) is composed of interleukins (IL)-29, IL-28A, and IL-28B and is induced in response to several viral pathogens. In the liver, type III IFN receptors are expressed at significant levels as a functional full-length form, suggesting intact type III IFN signaling as part of the intrahepatic innate immune response [13,14]. Genetic variants of the IFN- $\lambda 3$ and IFN- $\lambda 4$ locus are strongly associated with spontaneous clearance of HCV and with response to therapy with peg-IFN and RBV. The molecular mechanisms that link genetic variants near the IFN- $\lambda 4$ gene with constitutive activation of the endogenous IFN system in the liver are not entirely known, but it might involve an ongoing stimulation of the JAK–STAT pathway by IFN- $\lambda 4$ through the IFN- λ receptors on hepatocytes. In contrast to the innate immune response, which is induced within

hours to days after infection, the adaptive immune response against HCV is not detectable before 6–8 weeks and involves all components of the adaptive immune system, i.e., humoral antibodies, CD4⁺ T cells, and CD8⁺ T cells [10]. All these three components were shown to be associated with viral clearance. A well-coordinated interaction of the different immune cells might be essential for a successful immune response against HCV; however, little is known about the precise dynamic of this cross-talk [15]. HCV-specific T cells are recruited to the liver, and the viral replication is inhibited by both noncytolytic and cytolytic mechanisms. In about 20% of patients, the immune reaction during acute hepatitis C is strong enough to eliminate the infection. Immunocompetent HCV-infected individuals produce antibodies against epitopes within the structural as well as nonstructural proteins. Most of them, however, have no relevant antiviral activity, and only a small fraction of antibodies is able to inhibit virus binding, entry, or uncoating. These “neutralizing antibodies” target linear as well as conformational discontinuous epitopes mainly located within the envelope glycoproteins E1 and E2. While strong data indicate the neutralizing activity of these antibodies *in vitro*, their efficiency *in vivo* is less understood [10,15]. HCV elimination is associated with strong and sustained CD4⁺ and CD8⁺ cell responses that target multiple epitopes within the different HCV proteins and that remain detectable long after resolution of infection [10,16,17]. They act noncytolytically, by secreting antiviral cytokines such as IFN- γ , as well as cytolytically, through perforin secretion and by engaging the FAS/FAS-L pathway [15]. Despite the intervention of both innate and adaptive immune response in CHC, the virus is able to escape from these barriers through yet unknown mechanisms.

4. Epidemiology and world impact of HCV

HCV infection is one of the main causes of chronic liver disease worldwide, and according to recent estimates, until now more than 185 million people around the world have been infected. In addition, annually there are three million of new infected people, and among them 350,000 die every year due to HCV-related disorders [18–21]. The prevalence of HCV varies greatly, depending on the geographical area and the population considered: in Western Europe, it ranges from 0.4% to 3%; in Eastern Europe and the Middle East, it is higher but not precisely known [22]. The majority of the infected people reside in Asian countries (Taiwan, Mongolia, and Pakistan), sub-Saharan Africa (Cameroon, Burundi, and Gabon), and the Eastern Mediterranean (Egypt), which holds the highest frequency, with more than 20% [18]. HCV is a major global public health issue due to its high prevalence, long-term unpredictable disease progression, and low diagnosis and treatment response rates. Despite the fact that HCV infection rates are decreasing, the clinical and economic impact of chronic HCV infection is expected to considerably grow in the next decade since a large population of individuals that acquired the virus in the 1960s developed disease-associated health issues through to the 1980s [23]. The dual therapy, based on the administration of peg-IFN and RBV, is successful only in 40–50% of patients infected with the GT-1, while untreated individuals or who failed treatment are at risk of developing severe liver injuries such as cirrhosis, liver transplantation, and hepatocellular carcinoma (HCC) [24]. In Europe, there are 30,000 people on the transplant waiting list but only 12,000 procedures per year, and the average cost of liver transplant in the United States varies between \$139,000 and \$400,000 [25]. Although HCV can be successfully treated

by now using antiviral therapy based on the administration of new direct acting antivirals (DAAs), the economic burden of the disease, including complex regimens and the cost of treatment, remains high since health care costs continue to rise [26]. For this reason, many HCV-diagnosed patients around the world are left untreated or undertreated. A 2010 study performed on U.S. employments found that the cost of sick days and lower productivity per HCV-infected workers was US\$8,352 per year [25]. A U.S. survey by the American Gastroenterological Association (AGA) indicated that the cost for 30,000 outpatient visits for HCV infection amounted to US\$24 million in the 1998 [27]. The median cost for treating one patient with dual therapy (peg-IFN and RBV) ranges from €7,517 to €21,229, depending on the virus genotype, plus the costs of the new DAAs are about US\$70,100 per quality-adjusted life years (QALY) for mild fibrosis and US\$36,300 per QALY for advanced fibrosis [28].

5. Natural history of HCV infection

HCV transmission primarily occurs via parenteral routes. Before the 1990s, the main routes of transmission were unsafe blood transfusion procedures and injecting drug use. Currently, new infections are mainly due to the use of drugs and, to a lesser extent, to unsafe medical and surgical procedures, tattoos, and piercings. Distinctive HCV genotype distribution and prevalence worldwide are due primarily to differences in transmission routes and clinical care (Table 1) [29,30].

Patients
People who have received blood transfusions and solid organ transplant before 1992, or coagulation factor before 1987, or in countries where serological testing of blood donations for HCV is not routinely performed
Patients exposed to nosocomial infections such as employees in hemodialysis centers
Recipients of previously unscreened blood, blood products, and organs
Hemophiliacs
People with HIV infection
People exposed to unsterile medical or dental equipment in health care settings where infection control practices are substandard
Workers and other categories
Health care workers with occupational exposure to blood
Infants born from HCV-infected mothers
Injecting drug users and people using intranasal drugs
People receiving tattooing, body piercing, scarification procedures, and/or acupuncture with unsterile material
Prisoners
Sexual and household transmission are possible
10–40% with no identifiable risk factor

Table 1. Populations with high HCV prevalence or who have a history of HCV risk exposure/behavior

Acute HCV infections are often oligo- or asymptomatic. The long incubation period makes difficult to link related cases to the source of infection, and despite the high prevalence of disease, most infected people are unaware of their infection. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without HCC [31]. Spontaneous clearance in the chronic phase of the infection is rare and occurs only in 15–25% of cases. In 70–80% of infected patients, the virus persists and the infection becomes chronic. In most patients, CHC leads to different degrees of liver fibrosis, and one third (15–25%) of them could develop liver cirrhosis and HCC at a rate of 2–4% after 10 to 40 years (Figure 1) [10,18]. The progression of liver disease occurs over decades and is accelerated by alcohol consumption, diabetes/obesity, coinfections (human immunodeficiency virus [HIV] and hepatitis B virus), old age at the time of infection, cumulative exposure to hepatotropic viruses, and environmental hepatotoxins [32,33]. The extrahepatic manifestations of HCV infection include cryoglobulinemia, membranous glomerulonephritis, and some non-Hodgkin lymphomas [34]. In Europe, about 1/4 of HIV-infected patients have an HCV coinfection. Patients coinfectd with HIV/HCV have a higher risk of cirrhosis and AIDS and a higher overall mortality [35]. Thanks to the growing knowledge on the pathophysiology of the disease, the development of diagnostic procedures, and the improvements in therapy and prevention, the clinical care for patients with HCV-related liver disease has considerably advanced during the last years.

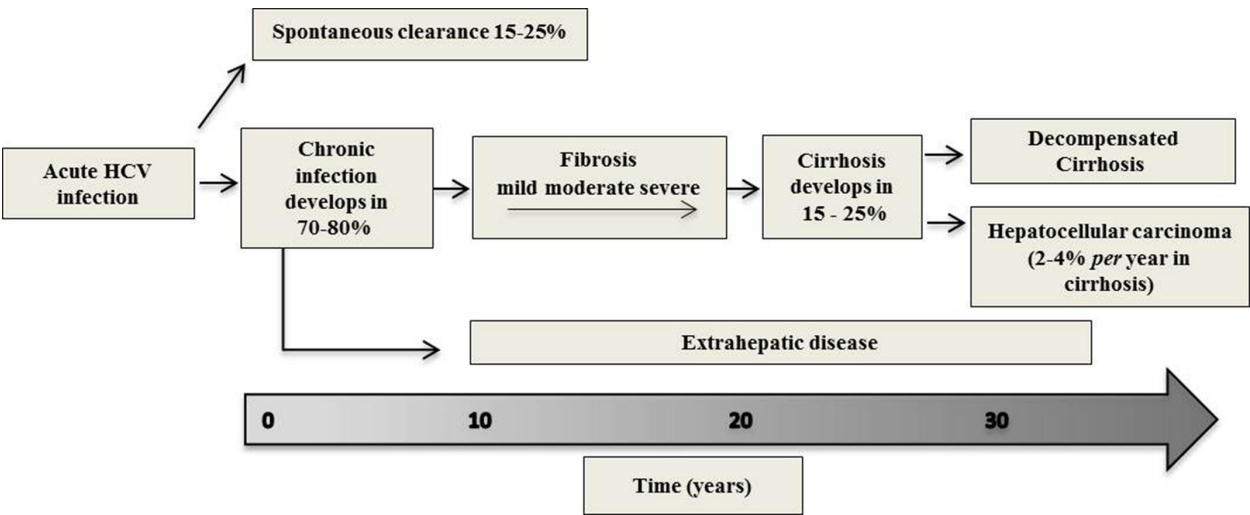


Figure 1. Natural history of HCV infection. In patients with HCV infection, the spontaneous clearance after the acute phase occurs only in 15–25% of cases; during the chronic phase, extrahepatic manifestations might occur. For patients who progress to decompensated cirrhosis, the survival rate at 5 years is about 50%, and among them, 2–4% per year develop hepatocellular carcinoma

6. Screening and diagnosis

Since many infected people are unknown to health care systems due to the asymptomatic nature of the disease, the management of HCV infection should focus not only on therapy but

also on the screening of carrier individuals in order to prevent transmission [36]. In the case of a newly acquired infection, the diagnosis of CHC can be made 4–6 months after viral infection [30]. The HCV serologic testing should be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/behavior. It is also important to consider the possibility of infection with other blood-borne viruses in subjects with HCV, and to offer screening for tuberculosis, hepatitis B virus, and HIV, especially in some groups at risk, such as prisoners and people who inject drugs [18,26]. The current diagnostic techniques for HCV infection are based on a range of tests, including the detection of anti-HCV by enzyme immunoassay in the majority of patients. The test for HCV-RNA by real time polymerase chain reaction is considered the best technique to confirm the presence of viremia and represent the gold standard in HCV diagnosis [lower limit of detection <15 international units (IU)/mL] playing a crucial role in patient management and for choosing the best therapeutic regimen [30,31].

Following spontaneous or treatment-induced viral clearance, anti-HCV antibodies persist in the absence of HCV RNA but might decline and finally disappear in some individuals [37,38]. Additional tests include HCV genotype and subtype determination and host genetics. The improved safety and efficacy of the new DAAs across genotypes could allow a simplified approach to pretreatment screening, without requiring further baseline tests [39].

7. Assessment of liver disease severity

Due to the particularly high cost of the new DAAs, in the last 3 years, the access to treatment has been restricted and strictly regulated. For this reason, the decision regarding treatment initiation with DAAs mainly focus on the assessment of liver disease severity. In particular, individuals at more advanced stages and with compensated cirrhosis benefit more than people with less advanced cirrhosis since they are at higher dying risk.

Well-established panels of direct and indirect biomarkers have been studied for the assessment of fibrosis progression and for the diagnosis of cirrhosis. Indirect biomarkers reflect liver function while direct biomarkers reflect extracellular matrix turnover and include many molecules involved in hepatic fibrogenesis. The most commonly used indirect serum biomarkers comprise the following: (i) the AST platelet ratio index [APRI = (AST/upper limit of normal) × 100/platelet count] that was extensively validated in chronic HCV; (ii) Fibrotest, a patented biomarker panel using five biochemical markers and two clinical parameters, which was validated in several etiologies of cirrhosis and in the monitoring of fibrosis progression; and (iii) FIB4, a biomarker panel using age, AST, platelet count, and ALT [FIB4 = (age × AST) / (platelets × √ALT)], originally developed and validated in a cohort of HIV/HCV-coinfected patients [40]. The blood tests needed for calculating APRI and FIB4 scores are inexpensive and are available at the health facilities that provide treatment for HCV infection since they are also used to monitor patients before and after the commencement of treatment [18,26]. Liver biopsy remains the reference method for grading the activity and histological progression (staging) of the disease [30,31,41]. However, because of its invasiveness, patient discomfort,

risk of complications, as well as the need for expert histological interpretation, transient ultrasound elastography (Fibroscan) is now used to assess liver disease severity prior to therapy at a safe level of predictability [42,43]. Fibroscan is a noninvasive method of measuring the mean stiffness of hepatic tissue, with hepatic rigidity considered a marker of progressive fibrosis. There are different scoring systems for assessing the severity of chronic liver disease. The major approach to classify CHC involves three separate considerations: (1) the etiology, which is determined on the basis of histological appearance and laboratory tests; (2) the severity and distribution of necroinflammatory activity; and (3) the degree of fibrosis [44]. The most common scoring methods to interpret a liver biopsy include the Metavir, the histologic activity index (HAI), also known as Knodell score, and the modified hepatic activity index (Ishak-modified Knodell score) [45].

Metavir is a scoring system used to assess inflammation and fibrosis by histopathological evaluation of a liver biopsy of patients with HCV. The scoring from A0 to A3 represents a grading system that gives an indication on the activity and degree of inflammation. The amount of inflammation is relevant since it is considered a precursor of fibrosis (Table 2). Metavir also includes a staging system that indicates the amount of fibrosis or scarring [46].

The Knodell score is a semiquantitative and reproducible histological scoring of liver biopsies, also commonly used for staging liver disease, that includes three categories of necroinflammatory activity: periportal injury with or without bridging necrosis, lobular injury, and portal inflammation. Lesions are assigned weighted numeric values that resulted in a combined score, the hepatic activity index (HAI) [47].

In the last years, the Knodell score has been partially replaced by the Ishak score, in which the major changes concern the modification of the HAI and the further division of necroinflammatory assessment in four categories [45].

Activity grade	A0	A1	A2	A3	
Definition	No activity	Mild activity	Moderate activity	Severe activity	
Fibrosis stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with few septa	Numerous septa without cirrhosis	Cirrhosis

Table 2. Metavir liver biopsy scoring system

8. Predictors of treatment response to HCV

Several patient and viral-related factors that can affect the severity of the disease, its progression, and treatment outcome have been identified. The chronicity rate in HCV infection appears to be lower in young individuals, and several studies highlight that young age (age <40 years) is associated with more sustained virological response (SVR) [33,48]. The female sex is associated with a higher SVR rate than that of males, using the standard peg-IFN and RBV dual therapy [49]. Obesity is also a relevant predictor of disease progression, and prospective

studies report that a body mass index of 25 kg/m² was associated with significant progression in the extent of fibrosis [50]. Furthermore, insulin resistance is extremely common in patients with chronic HCV infection and has been associated with increased disease severity, extrahepatic manifestations, and decreased response to antiviral therapy [51]. Many epidemiological studies showed an association between chronic HCV infection and the risk of developing type 1 and type 2 diabetes mellitus [52]. Taking into account the viral factors, HCV genotype is the strongest baseline predictor since there is a close correlation between the different genotypes and sensitivity to IFN-based therapies. GT-1 and GT-4 are intrinsically more resistant to IFN- α than GT-2 and GT-3, and for this reason, the viral clearance in patients who are IFN responders occurs much slower in GT-1 and 4, as compared to 2 and 3 [53]. Although viral load does not correlate with the severity of liver injury or the progression of the disease, a low baseline viral load (<600,000 IU/mL) is related with the SVR and the treatment outcome [54].

Genetic variations have long been sought to explain the differences in host antiviral response, and it is now well established that host genetics plays a role in the response to IFN-based therapy in HCV infection [55]. A number of polymorphisms related to the IFN gene (IL28B) have been involved in the immune response to HCV and appear to be strongly associated with SVR in all groups of patients [56]. There are three IL28B distinct genotypes known as CC, CT, and TT, which are strongly associated with race/ethnicity. People with the CC genotype have a stronger immune response to HCV infection than people with the CT or TT genotypes (called non-CC genotypes), and this polymorphism is strongly associated with a greater likelihood of spontaneous viral clearance [57]. In the context of peg-IFN/RBV therapy, the IL28B genotype could assist clinical decision making for the treatment of HCV infection. The first generation of DAAs, including nonstructural NS3/4A protease inhibitors, has shown promising outcomes when used in combination with peg-IFN/RBV in several clinical trials on GT-1-infected patients, with an SVR higher than the dual therapy [58,59]. The SVR rates in the SPRINT-2 and ADVANCE trials were higher in patients with CC (80% and 90%, in the two trials, respectively) compared with CT (71% and 71%) or TT (59% and 73%) [60–62]. It is not yet clear if IL28B polymorphism could still affect the treatment outcome with the interferon-free regimen since larger cohort sizes will be required to confirm its influence.

9. Current standard of care and future therapies for HCV infection

In the past few years, HCV therapy has quickly changed the natural history of this disease. Before 2011, the gold standard of therapy was based on the combination of peg-IFN and RBV that, however, acts by unspecific and not completely known mechanisms and exhibited low efficacy in some subgroup of population. The improvement of the knowledge on HCV life cycle allowed to identify innovative therapeutic targets and to develop new drugs known as direct acting antivirals (DAAs). These drugs target three of the main proteins involved in viral replication: the NS3/4A protease, the NS5B polymerase, and the NS5A. The addition of DAAs to peg-IFN and RBV and the development of new interferon-free regimen have dramatically increased clinical outcome leading SVR rates from 90 to 100% (Figure 2).

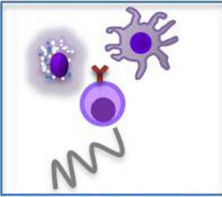






Therapeutic target		Drugs	Mechanism	Activity
Indirect Drugs		Interferons	Trigger intracellular signaling that enhance the host-specific and non-specific antiviral immune responses	All HCV genotypes
		Ribavirin	Not fully understood; likely has both direct and indirect effects on HCV virus replication	All HCV genotypes
Non-structural proteins				
Direct-Acting Antiviral Drugs	 RNA dependent RNA polymerase	Sofosbuvir (NI) Dasabuvir (NNI)	Inhibit the RNA-dependent RNA polymerase by binding to the catalytic site of HCV polymerase (NIs) or near the active site of the enzyme (NNIs)	All HCV genotypes
	 Viral Replication or assembly	Daclatasvir, Ledipasvir, ABT-267, MK8742, GS-5816, ABT-530	Not yet completely known; seem to inhibit viral RNA replication and assembly	All HCV genotypes
	 Membranous web formation	n.a.	n.a.	n.a.
	 Serine Protease	Simeprevir, Boceprevir, Telaprevir ABT-450, MK5172 ABT 493	Inhibit the HCV NS3/NS4 serine protease responsible for processing of HCV polyprotein and production of new infectious virions	Genotypes 1a and 1b
	 Protease	n.a.	n.a.	n.a.
	 Viral assembly	n.a.	n.a.	n.a.
	Structural proteins Core E1 E2		n.a.	n.a

Figure 2. HCV protein products, mechanism of action, and activity of anti-HCV drugs. NIs: nucleoside inhibitors; NNIs: nonnucleoside inhibitors; n.a.: not available.

9.1. Endpoints of treatment

The goal of HCV therapy is to eradicate infection, thus limiting or preventing the development of disease complications. The most important endpoint, accepted by regulatory agencies for assessing the efficacy of the therapy, is the sustained virological response (SVR) (Table 3). SVR is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. Achieving this result is associated with a reduced risk of disease progression in patients without cirrhosis, while those with cirrhosis remain at risk of life-threatening complications [30,31].

Responses to therapy	Features
Rapid virological response	Undetectable HCV RNA levels at week 4 of therapy, maintained until the end of treatment
Extended rapid virological response	Undetectable HCV RNA levels at weeks 4 and 12
Early virological response	HCV RNA detectable at week 4 but undetectable at week 12, maintained until the end of treatment
Delayed virological response	More than 2 log ₁₀ drop but still detectable HCV RNA at week 12, and undetectable at week 24, maintained until the end of treatment
Sustained virological response	Undetectable HCV RNA levels (<50 IU/mL), 24 weeks after completion of treatment
Partial response	More than 2 log ₁₀ IU/mL decrease in HCV RNA level from baseline at week 12 of therapy but still detectable at weeks 12 and 24
Null response	Less than 2 log ₁₀ IU/mL decrease in HCV RNA level from baseline at week 12 of therapy
Relapse	Undetectable HCV RNA levels at the end of treatment but detectable at any time within 24 weeks of follow-up
Breakthrough	Reappearance of HCV RNA at any time in the course of treatment

Table 3. Definition of responses to therapy according to the European Association for the Study of the Liver (EASL) (extracted from Conteduca et al. [75]).

9.2. Dual therapy: Pegylated-interferon and ribavirin

Until recently, the combination of peg-IFN and RBV was the “historical” standard of care for patients with HCV, and many regimens still contain one or both of these agents [8]. The IFNs are a family of proteins, naturally produced by cells of the immune system with antiviral, antiproliferative, and immunomodulatory activities. After administration, IFNs bind specifically to high-affinity receptors that are present on the surface of most cells, triggering a cascade of intracellular signaling responsible for the antiviral functions and immunomodulatory effects that enhance the host-specific antiviral immune responses [63]. However, in clinical practice, the efficacy of IFN is limited by short half-life and frequent administration (at least three times weekly, even better daily). These limitations have been resolved by developing a modified IFN conjugated with the polymer polyethylene glycol (peg). The introduction of pegylated forms of IFN- α has substantially improved SVR rates and pharmacokinetic profile, allowing once-weekly dosing without changing the safety profile [64]. RBV is an oral guanosine analog with broad antiviral activity against several RNA and DNA viruses. The exact mechanism of action has not yet been totally elucidated, although several hypotheses suggest that its biological action occurs through modest inhibition of viral replication, depletion of cellular guanosine triphosphate, immunomodulatory effects, and possible induction of viral mutagenesis [65]. The duration of combined therapy depends on genotype, viral load, and stage disease, with variable regimens from 24 to 48 weeks. Results from clinical practice showed that 45% of patients with GT-1 and GT-4 infection, 70–80% of those infected with GT-2

or GT-3, and 45–70% of patients with other genotypes achieved the SVR [66–72]. However, there were several limitations in treating patients with peg-IFN and RBV due to drug toxicities, low tolerability, or low efficacy (many patients do not respond or became intolerant) [69,70]. The safety profile is one of the limitations leading to dose reduction or treatment discontinuation. Adverse events caused by peg-IFN are fatigue, flu-like symptoms, depression, anemia, neutropenia, and thrombocytopenia, while those caused by RBV are blood and lymphatic disorder, nausea and vomiting, headache, anorexia, rash, and skin irritation [24,69].

9.3. NS3/4A inhibitors class

Protease inhibitors (PIs) act through reversible and covalent inhibition of the serine protease NS3/4A responsible for processing of HCV polyprotein and production of new infectious virions (Figure 2). These drugs can be structurally divided into two groups: linear tetrapeptide α -ketoamide derivatives and macrocyclic inhibitors. Generally, PIs have a remarkable antiviral activity and a low barrier to resistance and are selective against GT-1 infection. Furthermore, the most NS3/4A inhibitors interact with the cytochrome CYP3A4, one of the main enzymes responsible for drug metabolism, and this results in increased drug–drug interactions that can limit treatment regimen [8,73]. These limitations have been partially overcome by the advent of a new generation of PIs, which are also effective against genotypes other than the GT-1, and possess a higher barrier to viral resistance as well as lower propensity for toxicity and drug–drug interactions [8,74].

9.3.1. Telaprevir and Boceprevir

Telaprevir and boceprevir are the first generation of PIs approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Telaprevir and boceprevir have been licensed in combination with peg-IFN and RBV, for the treatment of GT-1 infection in naive and experienced patients with compensated liver disease. Telaprevir and boceprevir improved SVR from 49% to 75% in naive patients as compared to the dual therapy [7,75]. Although these therapies have increased clinical outcome, their use is limited by increased rate of adverse effects, including hemolymphopoietic disorders and other reactions related to gastrointestinal system (nausea, diarrhea, vomiting, hemorrhoids, proctalgia, and pruritus). Furthermore, the drugs have a low genetic barrier to resistance [68] and extensive drug–drug interactions that limit their use in transplanted or coinfecting patients [76–78].

9.3.2. Simeprevir

Simeprevir is a once-daily, second-wave protease inhibitor, licensed recently by the FDA and the EMA. This agent is indicated in association with peg-IFN and RBV for the treatment of GT-1 and GT-4 infection. This drug can be associated with sofosbuvir regardless of prior patient treatment history [79]. Simeprevir has a broad spectrum of activity against multiple HCV genotypes except for GT-3 [80]. Data from different trials show that it is highly effective and well tolerated. The most common adverse events are nausea, rash, pruritus, dyspnea, increment in bilirubin blood levels, and photosensitivity [8,74,79]. The NS3 Q80K polymorphism is commonly found in GT-1a viruses and is associated with resistance *in vitro* and

impaired response to simeprevir. It is therefore recommended that patients infected with GT-1a must be screened for the presence of Q80K to evaluate the use of another agent in case of positive result [81]. The activity of simeprevir has been validated in several phase II/III studies: QUEST I, QUEST II, PROMISE, ASPIRE, and RESTORE.

In the QUEST I and QUEST II studies, 785 naive patients with GT-1 infection were randomized to placebo or simeprevir plus peg-IFN and RBV for 12 weeks. Eighty percent of patients treated with simeprevir achieved SVR12 compared with 50% in the placebo arm [81,82]. The PROMISE study randomized 393 relapsers with GT-1 infection to simeprevir or placebo for 12 weeks with peg-IFN plus RBV or RBV alone for additional 12–36 weeks, on a response-guided therapy basis. In this trial, 79% of simeprevir treated patients achieved an SVR at 12 weeks compared with 37% of patients in the placebo arm [83]. The efficacy of simeprevir in patients with GT-1 infection was evaluated also in the ASPIRE study that confirmed these results [84]. Finally, in the RESTORE trial, the efficacy of simeprevir in GT-4 infection was established [85].

9.3.3. Paritaprevir

Paritaprevir is an NS3/NS4A protease inhibitor that has been licensed by the FDA and the EMA in combination with ritonavir, ombitasvir, and dasabuvir with or without RBV. Paritaprevir is metabolized primarily by cytochrome CYP3A4 and is used in combination with ritonavir, a potent CYP3A4 inhibitor, in order to improve the exposures at acceptable dosing frequency [86,87].

9.4. NS5A inhibitors class

The nonstructural NS5A protein is critical for the virus functions, having a role in viral replication and assembly, and performing complex interactions with cellular functions. Because of this crucial role, NS5A has been identified as a suitable target for viral inhibition (Figure 2). NS5A inhibitors have a high antiviral potency, a pan-genotypic activity, and a genetic barrier to resistance from medium to high. They also possess a good pharmacokinetic and a safety profile that allow once-daily dosing [8,75,88]. Although several NS5A inhibitors are in clinical development or already approved, the exact mechanism is not yet completely known [89]. Recent evidence reported that some of these drugs inhibit formation of the *membranous web* (Figure 2) that is thought to be the site of viral RNA replication [88,90]; other hypotheses suggest that NS5A inhibitors induce rearrangement of NS5A from endoplasmic reticulum-derived foci and limit hyperphosphorylation of this nonstructural protein [91–93].

9.4.1. Daclatasvir

Daclatasvir is the first NS5A inhibitor that is active at picomolar concentrations with broad coverage of HCV genotypes [89]. Daclatasvir has been recently approved in combination with sofosbuvir with or without RBV for the treatment of GT-1, GT-3, and GT-4 chronic hepatitis C in naive and experienced patients. Daclatasvir has a pharmacokinetic profile that allows once-daily dosing, and a low potential of causing drug–drug interactions with other medications

[94]. Daclatasvir was studied in various combinations with NS3 and NS5B inhibitors and with peg-IFN and RBV.

In a phase II study, 395 naive patients with GT-1 and GT-4 infection were randomized to receive two doses of daclatasvir (20 or 60 mg) in combination with peg-IFN and RBV compared with peg-IFN and RBV plus placebo. The SVR24 was achieved by 59.2% of patients receiving 20 mg, 59.6% in those who received 60 mg, and 37.5% in the placebo group. In patients with GT-4 infection, the SVR24 was achieved by 66.7% and 100% of those who received 20 mg or 60 mg daclatasvir, respectively, vs 50.0% in the placebo group [95].

In the COMMAND trial, 151 treatment-naive patients with GT-2 and GT-3 infection were randomly assigned to receive daclatasvir or placebo plus peg-IFN and RBV for 24 weeks. SVR24 was achieved by 83% in GT-2 infection and by 69% in GT-3 infection, vs 63% in control arm [96]. The treatment is well tolerated, and the main adverse events reported are diarrhea, fatigue, headache, and nausea. The most significant resistant associated variants are 31V and Y93H for GT-1b, and 31V, Y93H M28, and Q30 for GT-1a [97].

9.4.2. *Ledipasvir*

Ledipasvir is a potent NS5A inhibitor against GT-1, GT-4, and GT-5 infection but has lower activity against GT-2 and GT-3 infection [89]. Ledipasvir was recently approved in combination with sofosbuvir with or without RBV for the treatment of GT-1-, GT-3-, and GT-4-infected patients, naive or experienced, and for the advanced liver disease [98]. This combination is one of the most emerging interferon-free therapies that present a better safety profile than standard therapy and an elevated efficacy with SVR rates from 90% to 100%.

9.4.3. *Ombitasvir*

Ombitasvir is a novel potent NS5A inhibitor with a promising efficacy particularly in difficult-to-treat patients, in association with other DAAs [99]. This drug has been licensed by the FDA and the EMA in combination with paritaprevir/ritonavir and Dasabuvir with or without RBV. The efficacy of this drug was proved in several clinical trials both in association with peg-IFN/RBV and in interferon-free regimens. In a study of treatment-naive GT-1-infected patients, ombitasvir in combination with peg-IFN and RBV showed an early virological response in 25 out of 28 patients receiving the NS5A inhibitor compared with 6 out of 9 patients in the placebo group [89,99,100].

9.5. NS5B inhibitors class

NS5B protein is responsible for replication of HCV RNA and represents one of DAAs therapeutic target (Figure 2). NS5B RNA polymerase inhibitors can be divided into two distinct categories: the nucleoside inhibitors (NIs) and the nonnucleoside inhibitors (NNIs). NIs act by binding to the active site of the enzyme and are integrated into the growing RNA chain, causing chain interruption. Nonnucleoside inhibitors (NNIs) bind outside the active site, leading to the allosteric inhibition of RNA polymerase activity [8,75]. NIs have pan-genotypic activity and a medium–high barrier to resistance; NNIs have a low–medium activity against different

HCV genotypes as well as a low barrier to resistance. These differences are explicated on the basis of different mechanisms of action because NIs act in a highly conserved region of the HCV genome while NNIs bind only one of the four binding sites, and this results in a lower efficacy against the different HCV genotypes [7,75].

9.5.1. Sofosbuvir

Sofosbuvir is the first NI approved by the FDA and the EMA in combination with other antiviral drugs for the treatment of all HCV genotypes in adults [101]. Recently, sofosbuvir was approved as a fixed-dose combination in a single tablet with ledipasvir [98]. Sofosbuvir has a potent activity against all HCV genotypes, a high barrier to resistance, an excellent tolerability, and a very favorable pharmacokinetic profile. The addition of sofosbuvir to peg-IFN and RBV did not increase the frequency or severity of side effects [101,102]. The main adverse events reported in clinical trials are fatigue, headache, and nausea. *In vitro* resistance is linked to the development of an S282T mutation in the NS5B gene, although this should be confirmed in higher numbers of patients [7,8]. The efficacy of sofosbuvir was evaluated in patients infected with GT-1 to GT-6 chronic hepatitis C and was licensed on the basis of the following three studies: NEUTRINO, PROTON, and ATOMIC.

The NEUTRINO was a phase III, single-arm study that investigated the efficacy and safety of sofosbuvir with peg-IFN and RBV in 327 naive patients with GT-1, GT-4, GT-5, or GT-6 infection. SVR rates at 12 weeks were 90% for GT-1 infection, 97% for GT-4/GT-5/GT-6 infections, and 80% in patients with cirrhosis [103]. In the PROTON study, 147 GT-1-infected patients were treated with sofosbuvir or placebo in combination with peg-IFN and RBV for 12 weeks. SVR12 rates were achieved by 91% in sofosbuvir arm and 58% in the placebo group [8,104]. Finally, results from ATOMIC study confirmed the high efficacy of sofosbuvir in these populations [105]. The introduction of this drug in clinical practice has changed the clinical outcome achieving SVR over 90% especially in difficult to treat population as the GT-1-infected one.

9.5.2. Dasabuvir

Dasabuvir is a nonnucleoside inhibitor and will be used as a part of the all-oral interferon-free HCV therapy in combination with ombitasvir and paritaprevir/ritonavir. This combined therapy has been recently approved by the FDA and the EMA. This combination has shown high efficacy in several clinical trials and is one of the most promising interferon-free regimen. Dasabuvir was developed to treat GT-1-infected patients while is inactive toward GT-2, GT-3, and GT-4 infection. Dasabuvir is well tolerated, and the main adverse events recorded, when in combination with other DAAs, were mild such as headache and fatigue [106,107].

9.6. Future therapies for HCV infection: interferon-free regimen

During the last year, the advent of interferon-free regimen has dramatically changed the standard of care of anti-HCV therapy. These therapies include molecules with different

mechanisms of action, pan-genotypic activity that improve their safety, and efficacy profile, simplifying treatment duration. Several interferon-free combinations have been recently approved, and other trials are ongoing with different DAAs. Results from recent clinical studies established that a permanent cure from infection could be achieved with interferon-free combinations [20].

9.6.1. Sofosbuvir plus ribavirin

Sofosbuvir was the first drug licensed by the FDA and the EMA as part of interferon-free regimen. Currently, sofosbuvir is indicated in combination with RBV for the treatment of patients with GT-2 and GT-3 infection, even at advanced stages of the disease, while for all the other genotypes, it is recommended only in patients ineligible or intolerant to peg-IFN. Sofosbuvir-based treatment has been evaluated in several clinical trials [101]: FISSION, POSITRON, VALENCE, and FUSION.

FISSION was a randomized study that evaluated 12 weeks of treatment with sofosbuvir and RBV compared with 24 weeks of treatment with peg-IFN and RBV in 499 treatment-naïve patients with GT-2 or GT-3 infection. The SVR rates were 95% and 56% in GT-2- and GT-3-infected patients, respectively, for the treatment with sofosbuvir/RBV, vs 78% and 63% in the peg-IFN/RBV arm [103]. POSITRON study confirmed the clinical results obtained in FISSION study [108].

In the FUSION trial, the combination of sofosbuvir/RBV was evaluated in GT-2- or GT-3-infected patients, nonresponders to prior interferon-based treatment. SVR rates were 86–94% in patients with GT-2 infection and 30–62% in GT-3 infection, for 12 or 24 weeks of treatment, respectively [108]. The results obtained in the FISSION study for patients with GT-2 or GT-3 infection have been confirmed by the VALENCE trial [109].

Based on these studies, the combination of sofosbuvir and RBV showed high efficacy with SVR >90% in patients with GT-2 infection, while lower SVR rates were recorded in patients with GT-3 infection. This last population remains the most challenging group of patients to treat with interferon-free regimen.

9.6.2. Sofosbuvir/ledipasvir \pm ribavirin

Recently, the FDA and the EMA approved the fixed combination of sofosbuvir/ledipasvir with or without RBV for 12 or 24 weeks for the treatment of GT-1, GT-3, and GT-4 chronic hepatitis C in naïve and experienced patients and in patients who had liver peritransplant [98]. The efficacy of sofosbuvir/ledipasvir was evaluated in three phase III studies: ION-3, ION-2, and ION-1.

The phase III ION-3 study evaluated 8 weeks of treatment with ledipasvir/sofosbuvir with or without RBV and 12 weeks of treatment with ledipasvir/sofosbuvir, in 647 treatment-naïve noncirrhotic patients with GT-1 infection. The SVR12 was 94% in ledipasvir/sofosbuvir, 93% ledipasvir/sofosbuvir plus RBV in patients who received 8 weeks, and 95% in patients who received 12 weeks of ledipasvir/sofosbuvir. These results showed no benefits with the addition

of RBV in the regimen or with extension of the treatment duration to 12 weeks [110]. A similar rate of SVR was achieved in experienced patients with GT-1 infection in ION-2 and ION-1 studies, with clinical outcome ranging from 94% to 99% for subjects treated with ledipasvir/sofosbuvir \pm ribavirin [111,112]. The treatment is well tolerated, and the most common side effects are fatigue and headache [98].

9.6.3. Sofosbuvir plus daclatasvir \pm ribavirin

The combination of sofosbuvir plus daclatasvir with or without RBV for 12 or 24 weeks was evaluated in the AI444040 study in 211 patients infected with GT-1, GT-2, or GT-3, including treatment-naïve individuals and who had failed prior therapy with boceprevir or telaprevir. SVR12 was achieved in 98% naïve and experienced patients with GT-1 infection, 96% of those with GT-2 infection and 89% of those with GT-3 infection. The treatment was well tolerated, and the most common adverse events reported are fatigue, nausea, and headache. This results indicated that sofosbuvir plus daclatasvir is efficacious in GT-1-, GT-2-, or GT-3-infected patients and in nonresponders with GT-1 infection [94,113]. This therapeutic approach is now being tested in a phase III study, in subjects with GT-3 infection [114].

9.6.4. Sofosbuvir plus simeprevir \pm ribavirin

The safety and efficacy of combined oral sofosbuvir plus simeprevir was evaluated in the COSMOS study. In this trial, 168 patients (treatment-naïve patients and previous nonresponders) were randomized in two cohorts on the base of METAVIR scores (F0–F2 in cohort 1, F3–F4 in cohort 2) to receive 12 or 24 weeks of simeprevir and sofosbuvir with or without RBV. SVR was achieved by 92% in cohort 1 and 94% in cohort 2. This study suggested that the addition of RBV and treatment duration for 24 weeks did not clearly improve SVR rates. This combination therapy was well tolerated, and the most common adverse events were fatigue, headache, and nausea [115].

9.6.5. 3D regimen: paritaprevir/ritonavir, ombitasvir, dasabuvir \pm ribavirin

The multitarget therapy, which includes all-oral combination of paritaprevir/ritonavir, ombitasvir, and dasabuvir, is one of the most promising interferon-free therapies. Paritaprevir/ritonavir and ombitasvir are coformulated as fixed combination in a single tablet. The therapeutic regimen “all in one” is completely oral, without interferon, and is the unique that provides three antiviral agents with direct action, each characterized by a different mechanism of action. The 3D regimen \pm RBV is indicated for 12 or 24 weeks for the treatment of patients with GT-1 infection, while only paritaprevir/ritonavir and ombitasvir are indicated in GT-4 infection. The 3D regimen is also indicated in combination with RBV for 24 weeks in liver transplant recipients with GT-1 infection, in patients coinfecting with HIV-1, and in patients receiving replacement therapy with opioids [116,117]. The safety and the efficacy of this regimen were based on the results of six clinical trials: SAPPPIRE I, SAPPPIRE II, PEARL II, PEARL III, PEARL IV, and TORQUOISE II.

In the phase III SAPPHERE I study, 631 treatment-naïve adults with GT-1 infection were treated for 12 weeks with 3D regimen in combination with RBV. The overall SVR12 was 96% [118].

The SAPPHERE-II trial was conducted in 394 experienced patients with GT-1 infection without cirrhosis. The SVR rates were 95.3% among patients with a prior relapse, 100% among patients with a prior partial response, and 95.2% among patients with a prior null response [119].

The PEARL-III and PEARL-IV studies assessed the need to include RBV in the 3D regimen in treatment-naïve adults with GT-1 infection. Clinical results showed that SVRs are similar in GT-1a infection (99.5% *vs* 99% with or without RBV, respectively), while patients with GT-1b infection achieved higher SVR12 in RBV group (97.0% *vs* 90.2%, with or without RBV, respectively) [120]. Similar results were obtained in the PEARL-II, in experienced patients with GT-1b infection [121]. The efficacy of paritaprevir/ritonavir and ombitasvir in treatment-naïve or experienced patients with GT-4 infection was proved in the PEARL-I. In this trial, 90.9% of naïve patients treated with 3D regimen without RBV and 100% of naïve and experienced patients treated with 3D regimen plus RBV achieved SVR12 [122].

In the TURQUOISE-II study, the efficacy and the safety of 12 or 24 weeks with 3D regimen with RBV were assessed in patients with advanced disease and GT-1 infection. Ninety-two percent of patients achieved SVR rates at 12 weeks, *vs* 96% at 24 weeks. Experienced patients with GT-1a infection had a better response from 24 weeks of treatment [123]. The resistance profile observed in these clinical trials seems to have little impact on the likelihood of achieving SVR, given the low virological failure rates recorded. The 3D regimen has shown high efficacy in patients with GT-1 infection (90–100%) and is well tolerated. The main adverse events reported are moderate, mainly pruritus, fatigue, and headache [117,118]. This interferon-free regimen is now being tested in different clinical trials in association with other DAAs.

New interferon-free combinations are under investigation in phase II/III clinical trials. New compounds seem to have a more potent activity *vs* different genotypes than the DAAs of second generation. The aim of these new therapies is to treat HCV infection through shorter regimen. Grazoprevir and elbasvir \pm sofosbuvir and sofosbuvir and ledipasvir plus GS-9451 are the most promising combination in clinical development. A six-week interferon-free oral treatment regimen for HCV GT-1 infection will be likely available in the near future [124–127].

9.7. Special population

9.7.1. Liver transplanted patients

HCV infection is one of the risk factors of liver transplantation and an important cause of morbidity and mortality in these patients [128]. HCV infection recurrence occurs in 50% of subjects with detectable HCV RNA at the time of liver transplantation [31,129]. Dual therapy based on peg-IFN/RBV was the standard of care and is associated with low SVR rates at 24 weeks (20–25%). Telaprevir and boceprevir improved SVR until 67%, but drug–drug interaction with immunosuppressive agents and serious adverse events can limit their use [8,130,131]. The introduction of DAAs has improved the efficacy of HCV therapy in patients before and after liver transplantation.

The first interferon-free regimen evaluated in pretransplant setting was 48 weeks of sofosbuvir and RBV for all HCV genotypes. The posttransplant follow-up showed that sofosbuvir and RBV prevented recurrence of HCV infection in 70% of patients [132]. Similar SVRs were obtained in patients that had received liver transplant and then relapsed. The safety profile is better than standard therapy on the base of adverse events reported [133,134].

The SOLAR-1 Phase II study analyzed the combination of sofosbuvir and ledipasvir for 12 or 24 weeks, in naive and experienced patients with a relapse of GT-1/GT-4 infection after liver transplantation. The results showed that 96–98% of patients with F0-F3 fibrosis, 96% with Child–Pugh–Turcotte A cirrhosis, 85–83% with Child–Pugh–Turcotte B cirrhosis, and 60–67% with Child–Pugh–Turcotte C achieved the SVR12. The treatment was generally safe and well tolerated [135]. Finally, in the CORAL-I study, the safety and the efficacy of 24 weeks of 3D regimen with RBV were studied in 34 GT-1-infected liver transplant recipients with none or mild fibrosis. The SVR was achieved in 97.1% of patients [136].

9.7.2. HIV-coinfected patients

Due to shared modalities of transmission, the infection with HCV is often widespread among HIV-infected people. In the last decade, the rate of HCV coinfection was increased, and it has been estimated that about 15–30% of HIV-infected patients are also infected with HCV. HIV/HCV-infected patients are more difficult to treat since the coinfection decrease HCV clearance. The standard of care of these patients was the combination of peg-IFN and RBV, but the coadministration of several agents leads to increased drug–drug interaction and adverse events and requires dose adjustment [137,138]. Similarly to that reported for HCV monoinfected patients, the development of DAAs and interferon-free regimens has substantially increased the treatment outcome. The combination of sofosbuvir and RBV was explored in two studies. PHOTON-1 showed that 76%, 88%, and 67% of treatment-naive patients with GT-1, GT-2, or GT-3 infection, respectively, achieved the SVR12. Sofosbuvir has minimal or none interactions with a wide range of antiretroviral drugs, and treatment was well tolerated [139,140]. Similar results have been obtained from PHOTON-2 [141]. The combination of sofosbuvir and ledipasvir was evaluated in the ERADICATE study. In this trial, 100% of untreated and antiretroviral-treated patients achieved the SVR12 [142]. Finally, the results from TURQUOISE-I study showed that 93.5% of patients achieved SVR12 with 3D regimen plus RBV [143].

10. Conclusions and challenges for the future

The advent of DAAs and interferon-free strategies has substantially improved the clinical outcome in HCV therapy. Some interferon-free regimens have recently been licensed, and some other are in clinical development. These new combinations have shown high SVR, ranging from 90% to 100% even with shorter courses (8–12 weeks) of treatment, especially in low responsive population with dual and triple therapies. Current studies focus on the clinical

development of a new generation of DAAs, such as the combination of ABT 493 and ABT 530, sofosbuvir, and GS-5816, grazoprevir, and elbasvir, which will be available in the near future as therapeutic strategies with high efficacy and short regimen (4–8 weeks). However, both scientific and economic unresolved issues are still present.

For the scientific perspectives, new and larger clinical studies are required in subjects infected with GT-3, in treatment-experienced patients and at advanced stages of the disease, which remain the most difficult subpopulations to be treated [144,145].

From the economic point of view, even though the new medications for hepatitis C are effective disease modifiers and have the potential, in a long-term perspective, to eradicate the pathology, the costs of new treatments are unlikely to be sustainable for the NHSs. Indeed, new pharmaceutical policy and a global commitment are required to improve strategies of treatment and price negotiation with pharmaceutical companies to move from a theoretical cost-effectiveness approach to a practical cost-sustainable reality. Even if curing hepatitis C saves lives and prevents a lot of downstream health care costs related to the progression of the disease, including liver cancer or requirement of transplant, payers and politicians are in an uproar for a variety of reasons, not least the fact that the drug is priced much higher in the United States than in the rest of the world. For example, in Europe, where the government negotiates the price, the cost of sofosbuvir is on the order of \$55,000/patient. The ongoing discussion about the sustainability of the new treatments demonstrates the limit of the current health technology assessment classical approach. Indeed, the new products can be cost-effective in a long-term perspective, considering the avoidance of further hospitalization and medicalization costs related with transplantation. Until it will not be possible to reorganize the complete process of therapy, to be able to capitalize the expected savings, the cost-effectiveness evaluation will remain just a theory, posing concrete challenge to the sustainability of NHS systems. On the other hand, the proposed cost of treatment is still considered too high in relation to the prevalence of the pathology. This situation has opened the discussion on the necessity to find new reimbursement approaches and new level of cooperation between different States. In Europe, for example, bracket list price (min–max) for sofosbuvir has been proposed, to be adjusted for instance by GDP/Pro-capita income (e.g., differential price), prevalence (price/volume), and/or adaptive reimbursement considering genotyping, subclusters, and time to event. None of the possible solutions have been implemented in a coordinated manner, but the access to HCV new treatments stimulated, among health care decision makers, the consciousness of the need of a new global synergistic approach.

Author details

P. Pierimarchi*, G. Nicotera, G. Sferrazza, F. Andreola, A. Serafino and P.D. Siviero

*Address all correspondence to: pasquale.pierimarchi@ift.cnr.it

Institute of Translational Pharmacology, National Research Council of Italy, Rome, Italy

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