Chapter 4

Hepatitis C — Overview and Update in Treatment

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Additional information is available at the end of the chapter

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Abstract

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide, making it a major public health issue. The World Health Organization (WHO) estimates a worldwide prevalence of 3%. Each year, three to four million people are newly diagnosed with HCV, and it remains endemic in many countries of the world. According to the WHO, there are at least 21.3 million HCV carriers in Eastern Mediterranean countries, a figure close to the combined number of estimated carriers in the Americas and Europe. The purpose of this chapter is to give an overview and update in treatment of HCV patients by a broad search of published literature on aspect of epidemiology, natural history, risk factors, diagnosis and treatment of HCV, graded on the best available evidence. All that to improve HCV patient care, and to promote and improve the multidisciplinary care required in the treatment of these patients.

Keywords: HCV, hepatitis C treatment, sofosbuvir, Sovaldi, daclatasvir, ledipasvir/sofosbuvir, Harvoni, Viekira Pak, Viekirax, Exviera, simeprevir

1. Introduction

Hepatitis C virus (HCV) infection is one of the main causes of progressive liver disease worldwide, making it a major public health issue. World Health Organization (WHO) estimates indicate that more than 185 million people around the world have been infected with HCV, of whom 350,000 die each year [1].

HCV induces chronic infection in up to 80% of infected individuals. One third of those who become chronically infected are predicted to develop cirrhosis or hepatocellular carcinoma. Despite its high prevalence, most people infected with the virus are unaware of their infection.

The purpose of this chapter is to give an overview on HCV and existing treatments and to outline recent innovations in the treatment of HCV patients. To do this, a broad search of the published literature has been undertaken. The search included epidemiology of HCV, its natural history, the risk factors involved, as well as the diagnosis and treatment of HCV, all of which have been graded on the best available evidence. The ultimate purpose is to improve HCV patient care and to promote and encourage the multidisciplinary care required in the treatment of these patients.

2. Epidemiology

In most countries, surveys undertaken to establish the prevalence of HCV have focused on specific groups of individuals, for example, drug users, those indulging in high-risk sexual behavior, and blood donors who are not representative of the general population. Consequently, global estimates of HCV prevalence in the year 2008 are still not accurate [2].

Overall, the available data suggest that 130-170 million individuals are infected with HCV (approximately 2.2-3.0%) worldwide, with its highest prevalence occurring in Eastern Mediterranean and African regions [2,3].

Previously undertaken analyses on global, regional, and country levels have mostly failed to estimate the correct HCV disease burden with studies based on age distribution and active infection. Most country-level studies have been carried out on the adult population; however, when these estimates were applied to a country's entire population, the disease burden was probably overestimated. In addition, studies focused on anti-HCV (antibody positive) testing overestimated the disease burden because they often included those subjects who have been cured, either spontaneously or after treatment [4].

Globally, genotype 1 (G1) has been found to account for 46% of all anti-HCV infections among adults, making it the most common, followed by G3 (22%), G2 (13%), G4 (13%), G6 (2%), and G5 (1%). Undefined or combination genotypes accounted for 3% of total HCV infections [4]. Genotype 1b was the most common subtype, accounting for 22% of all infections. However, significant regional, country, and local variations were found to exist. Infections in North America, Latin America, and Europe were predominately G1 (62-71%), with G1b accounting for 26%, 39%, and 50% of all cases, respectively. North Africa and the Middle East had a large G4 population (71%), which was attributable to the high prevalence of G4 in Egypt. When Egypt was excluded, genotype 4 accounted for 34% of all infections, and the genotype distribution of this region was dominated by G1 (46%). Asia was predominately G3 (39%) followed by G1 (36%), largely driven by the HCV infections in India and Pakistan. G1b accounted for 25% of all infections in this region. In Australasia, G1 dominated (53%), followed by G3 (39%). G1b was present in 16% of cases [4].

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3. Virology

The hepatitis C virus is a hepatotropic RNA virus of the genus *Hepacivirus* in the Flaviviridae family, originally cloned in 1989 as the causative agent of non-A, non-B hepatitis [5,6,7]. HCV is a positive-sense, single-stranded enveloped RNA virus approximately 9600 nucleotides in length. Approximately 10^{12} viral particles are generated daily in chronically HCV-infected patients [5,8]. The genome is organized to include nontranslated RNA segments (NTRs) at 5 and 3 ends and a single large open reading frame (ORF) encoding a giant 327 kDa polyprotein that is processed by cellular and virally encoded proteases into three structural proteins (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [9].

The HCV 5 NTR contains 341 nucleotides located upstream of the coding region and is composed of four domains (numbered I to IV) with highly structured RNA elements, including numerous stem loops and a pseudoknot. The 5 NTR also contains the internal ribosome entry site (IRES), which initiates the cap-independent translation of HCV genome into a single polyprotein by recruiting both viral proteins and cellular proteins such as eukaryotic initiation factors (eIF) 2 and 3 [5].

The core protein is the viral capsid protein with a length of 191 amino acids (p21c). It can be further cleaved to generate a smaller 179-amino-acid core protein (p19c). The core protein has numerous functionalities involving RNA binding, immune modulation, cell signaling, oncogenic potential, and autophagy [5,9,10]. E1 and E2 are the two viral envelope proteins that surround the viral particles. p7 contains two transmembrane domains and is required for viral assembly and release. NS2 is the viral autoprotease that likely contains at least four transmembrane domains and plays a key role in viral assembly, mediating the cleavage between NS2 and NS3 [5,9,11,12]. NS3 protease plays a critical role in HCV processing by cleaving downstream of NS3 at four sites (between NS3/4A, NS4A/4B, NS4B/NS5A, and NS5A/NS5B) [5,9]. NS4A is a cofactor for the NS3 protease, and NS5B is the viral RNA polymerase. The functions of NS4B and NS5A are not totally clear, but they are probably involved in viral RNA replication and pathogenesis. All of these HCV proteins are believed to form replication complexes on intracellular membranes for either viral morphogenesis or RNA replication [5,9,13-15].

4. Natural history and clinical presentation

Hepatitis C is a heterogeneous disease with considerable morbidity and mortality rates. More than 80% of infected individuals develop chronic infection; the remaining 10-20% develop spontaneous clearance with natural immunity. The acute infection has an incubation period of 7 weeks (range, 4-20 weeks) and is symptomatic in only 20% of patients and rarely severely icteric. Serum aminotransferase levels generally increase to more than 10 times the normal range and go back to normal once the disease symptoms resolve themselves. HCV antibodies usually develop at the time of onset of symptoms. HCV RNA appears even earlier, during the incubation period, with an increase in titer at the time of the manifestation of symptoms, and

then disappears once the disease disappears. Once acute HCV infection has established itself, around 85% of patients develop chronic infection, which is generally asymptomatic. In these patients, HCV RNA remains present and in approximately 75% of patients, alanine aminotransferases (ALT), and aspartate aminotransferases (AST) remain elevated at more than 1.5 times the upper normal limit. The course of chronic hepatitis C is variable, with vague, intermittent, and nonspecific symptoms of chronic fatigue and malaise, which usually present in less than 20% of patients. Extrahepatic manifestations of HCV, including glomerulonephritis and cryoglobulinemia, can develop in a small percentage of patients. The development of progressive liver injury, fibrosis, and cirrhosis can occur in 20% to 30% of chronically infected patients over a period of 20-30 years. In patients presenting with chronic hepatitis C, fibrosis progression is extremely variable over time and can be partially predicted based on the age of the patient at infection, disease duration, liver histologic activity and stage of fibrosis, and ALT profile. However, it is often difficult to predict clinical outcomes in individual cases. In patients who have developed cirrhosis, the 5-year risk of decompensation is between 15% and 20% and that of hepatocellular carcinoma around 10%. The relationship between virus load, HCV genotype, quasi-species variability, and progression of liver disease is controversial. Acquired infection after age 40 years, being male, excessive alcohol consumption, hepatitis B virus (HBV) or HIV coinfection, steatosis, and immunosuppressed state have all been identified as cofactors associated with progression of fibrosis and development of cirrhosis. Once cirrhosis develops, symptoms are more common, and the signs of end-stage liver disease can appear, manifesting themselves as jaundice, weakness, wasting, and gastrointestinal bleeding. The incidence of developing hepatocellular carcinoma is 2-5% per year in patients with hepatitis C-related cirrhosis. Thus, this important liver disease has protean manifestations but is often insidious and can often lead to end-stage liver disease that needs liver transplantation, despite the presence of few overt symptoms and signs of illness [16-20].

5. Risk factors

The risk factors for the transmission of HCV infection vary substantially between countries and geographic regions. HCV is spread primarily by contact with blood and blood products. With the introduction in 1991 of routine blood screening for HCV antibodies and improvements in the test in mid-1992, transfusion-related hepatitis C has virtually disappeared. Illicit use of injectable drugs is currently the main source of HCV infections in most developed countries (e.g., Western Europe, US) and is becoming a major source of infection in transitional economy and developing countries, accounting for 40% or more of those infected. Of the estimated 16 million people in 148 countries who actively inject drugs, 10 million are infected with HCV [2,21,22]. In developing and transitional economy countries, the nosocomial transmission of new HCV infections is a major problem because of the reuse of contaminated or inadequately sterilized syringes and needles used in medical, paramedical, and dental procedures, with an estimated 2.3-4.7 million new infections occurring each year [2,23-25]. In patients on chronic hemodialysis, overall, the current prevalence of HCV is below 5% in most of Northern Europe, around 10% in most of Southern Europe and the US, but between 10%

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and 50% and up to 70% in many parts of the developing world, including many Asian, Latin American, and North African countries. It is important to emphasize that the prevalence of HCV is highly variable from unit to unit within the same country, with recent reports from some dialysis units in the US reporting a prevalence above 20% [26]. The risk of transmission of HCV from a mother to her child occurs in 4-8% of births to women with HCV infection and in 17-25% of births to women with HIV and HCV coinfection. The risk posed to the infant from breastfeeding is negligible, and nonsexual intrafamilial transmission is very rare [27,28]. The risk of heterosexual transmission is low, while recent data indicate that promiscuous male homosexual activity is related to HCV infection [29]. Folk medicine practices, including acupuncture and ritual scarification, as well as body piercing, tattooing, and commercial barbering are potential modes for transmission of HCV infection when performed without appropriate infection control measures [30,31].

6. Laboratory testing

6.1. Serologic and molecular assays

The test for anti-HCV is usually performed in the presence of an elevated ALT level and a positive history of risk factors for HCV infection, or physical findings suggest the presence of chronic liver disease. WHO recommends that HCV serology testing be performed on individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure and/or behavior rather than at the time of presentation with symptomatic disease. The application of this recommendation will require taking into consideration which populations meet these criteria. In some countries with a high seroprevalence of HCV or a low level of infection control, HCV testing might be recommended for the general population. Clearly, this would have significant resource implications [1]. Diagnosis of HCV infection is based on the detection of anti-HCV antibodies by enzyme immunoassay and the detection of HCV RNA by a sensitive molecular method, ideally a real-time PCR assay. These assays have no role in the assessment of disease severity or its prognosis [32,33]. Genotyping is useful in epidemiological studies, and also in clinical management, for predicting the likelihood of response and determining the optimal duration of therapy. Several commercial assays are available to determine HCV genotypes using direct sequence analysis of the 5 noncoding region, which includes Trugene 5 NC HCV genotyping kit, reverse hybridization analysis using genotype-specific oligonucleotide probes located in the 5 noncoding region, INNO-LiPa HCV II, and Versant HCV Genotyping Assay 2.0 [34,35].

6.2. Defining disease severity

Laboratory tests that are commonly obtained following the initial diagnosis of chronic hepatitis C include liver enzymes and function tests, a complete blood cell count, tests for coinfection with HBV or HIV, tests for immunoglobulin G antibody to hepatitis A virus (anti-HAV) to determine if immunity is present or if vaccination is recommended, and antinuclear antibody to exclude coexistent autoimmune hepatitis.

Elevated blood levels of liver enzymes ALT and AST occur when the membrane of the liver cells is damaged and liver enzymes leak into the blood stream, thus indicating ongoing liver injury. The degree of elevation of liver enzymes present in the blood correlates with the severity of liver cell injury. However, blood levels of liver enzymes do not correlate with the degree or severity of hepatic fibrosis. The important tests that reflect liver synthetic function are serum bilirubin, albumin, and international normalized ratio (INR). Abnormal serum albumin, bilirubin, or prothrombin time may be seen in the setting of impaired hepatic synthetic function. Some models used to evaluate liver disease severity are helpful for the assessment of liver function, for example, the model for end-stage liver disease (MELD). The MELD score was adopted by UNOS in 2002 for use in deceased donor liver allocation for adults with cirrhosis. MELD is a prospectively developed and validated chronic liver disease severity scoring system that uses a patient's laboratory values for serum bilirubin, serum creatinine, and INR to predict a 3-month survival [36]. The MELD equation that is currently used by UNOS for prioritizing allocation of deceased donor livers for transplantation is as follows: MELD = $3.8*\log_e$(serum bilirubin [mg/dL]) + $11.2*\log_e$(INR) + $9.6*\log_e$(serum creatinine [mg/dL]) + 6.4. Patients with the combination of serum creatinine ≤1 mg/dl, serum bilirubin ≤1 mg/dl, and INR ≤1 will receive the minimum score of 6 MELD points. In addition, UNOS has set an upper limit for the MELD score at 40 points. However, there is no need to go through the above time-consuming equation because several online tools are available for calculating the MELD score [37-39].

7. Tests of fibrosis

7.1. Noninvasive laboratory tests

Noninvasive tests of hepatic fibrosis are used for the staging of fibrosis in patients with chronic liver disease. The tests are often used to differentiate patients with significant fibrosis (F2 to F4) from those with minimal or no fibrosis (F0 to F1). There are four commercial serum marker systems that have been validated: FibroTest/FibroSure (marketed in the United States by LabCorp), Hepascore (Quest Diagnostics), FibroSpect (Prometheus Corp), and the European Liver Fibrosis Study Group panel (not available in the United States). In addition, the aspartate aminotransferase-to-platelet ratio (APRI) has also been studied. The APRI has the advantage of being easily calculated using data available from routine laboratory tests.

All the serum tests have limitations: (a) they typically reflect the rate of matrix turnover, not deposition, and thus tend to be more elevated when there is high inflammatory activity. By contrast, extensive matrix deposition can go undetected if there is minimal inflammation. (b) None of the markers are liver specific, and concurrent sites of inflammation may contribute to serum levels. (c) Serum levels are affected by clearance rates, which may be impaired due to either sinusoidal endothelial cell dysfunction or impaired biliary excretion. (d) They are surrogates, not biomarkers [40].

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7.2. Elastogram (Fibroscan)

Fibroscan can quantify fibrosis in the liver by means of elastography. Tissue elasticity is acquired through pulse-echo ultrasound, measuring shear wave velocity, the S-wave. The wave travels faster in less elastic and stiff livers. Results of liver elasticity are expressed in kilopascals (kPa). The scan can be performed easily; it is inexpensive and produces no side effects. The position of the patient is similar to when performing a liver biopsy, that is, on the back, with the right hand under the head. Patients only feel the probe pressure in the intercostal space without anticipated pain. It is possible to measure liver elasticity from different angles in the right as well as the left lobe. A liver stiffness measurement using Fibroscan is reproducible and independent of the operator, and explores a volume of liver parenchyma, which can be approximated to a cylinder of 1 cm in diameter and 4 cm in length. This volume is 100 times larger than the biopsy specimen volume and is thus much more representative of the entire hepatic parenchyma. Some extensive studies have demonstrated that the measurement of liver stiffness with Fibroscan is a good alternative for liver biopsy. The amount of fibrosis can be quantified very easily and reliably and is feasible in more than 95% of the patients. Obesity, ascites, and narrow intercostal spaces are physiological boundaries that can hamper the accuracy of the test. Acute hepatitis and liver congestion as in cardiac failure can cause false high scores, and they need to be ruled out before carrying out Fibroscan. Sometimes it may be virtually impossible to take measurements in such patients [41, 42]. Fibroscan value ranged from 2.4 to 75.5 kPa with a cutoff value of 7.1 kPa for $F \geq 2$, 9.5 kPa for $F \geq 3$, and 12.5 kPa for $F = 4$ (according to Metavir histological classification system) [41, 43]. One of the studies comparing elastography to histological examination on 327 patients concluded that liver stiffness measurements and fibrosis grades correlated well, with increasing reliability in more extensive fibrosis ($F \geq 3$) or cirrhosis. It was impossible to determine a cutoff value to differentiate between F0 and F1 by Fibroscan [41,44].

7.3. Liver biopsy

Percutaneous liver biopsy is the gold standard for grading and staging of liver disease, which can help to determine the extent of progress of hepatic fibrosis and inflammation. It is important in clinical practice, where it may reflect the severity of liver disease and predict response to treatment. Liver biopsy is an invasive procedure associated with discomfort and, in rare cases, with serious complications. The accuracy of liver biopsy is limited and prone to sampling error and interpretational variability. Although this procedure continues to be recommended, current practice is changing for two main reasons: first, treatment is being shown to be more effective, and second, biochemical tests, serological tests, and elastograms can all provide a great deal of information on disease progression. Pathologists can increase the importance and utility of liver biopsy in chronic hepatitis C, providing information not only on the stage of fibrosis and necro-inflammatory activity but also on the grade of steatosis and iron accumulation, which are implicated in disease progression. Moreover, other diseases, such as steatohepatitis and hereditary hemochromatosis can be identified by liver biopsy. Nevertheless, the use of serological and radiological tests will reduce the indications for liver biopsy [45].

8. Hepatitis C treatments

The ultimate goal of treatment in patients with chronic HCV is to eradicate HCV RNA, which is associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, hepatocellular carcinoma rates, and liver-related complications.

Since interferon-alpha (IFN-α) was first introduced for treatment of non-A, non-B hepatitis 1990, therapy for patients with chronic HCV has improved dramatically. Sustained virological response rates (SVRs) have increased from 5% to 10% with standard interferon therapy, to over 40% when standard interferon is combined with ribavirin. The modification of interferon (pegylation) to improve its pharmacokinetics has further increased rates of SVR. Two types of pegylated interferon, pegylated interferon α2a and pegylated interferon α2b,which differ in their pharmacokinetics and chemical properties, were approved by the FDA in 2001. Treatment with combined pegylated interferon and ribavirin may result in SVR in 42% to 52% of genotype 1 infected patients, 70% to 80% of genotype 2 or 3 infected patients, and 54-68% of genotype 4 infected patients [46,47].

The landscape of treatment for HCV infection has evolved substantially since the introduction of highly effective HCV protease inhibitor therapies, namely, boceprevir and telaprevir, in 2011. Both drugs were approved as directly acting antiviral treatments for use in HCV genotype 1 infection, in combination with pegylated interferon and ribavirin. These NS3/4A protease inhibitors have been shown to substantially increase rates of SVR to 59-75% in both treatment-naive and previously treated patients, compared with dual therapy [48-52]. Although their development was a major advance, both agents are associated with significant toxicity, numerous drug-drug interactions, and low response rates in those patients with cirrhosis and nonresponders to previous treatment. In addition, boceprevir and telaprevir required the addition of pegylated interferon and ribavirin for 24 to 48 weeks, which markedly increased the overall cost of therapy, and are associated with the emergence of resistance-associated variants in the majority of patients who fail treatment [53].

In 2013 and 2014, the FDA approved new direct acting antiviral treatments, including second generation protease inhibitors, NS5A inhibitors, and NS5B RNA-dependent RNA polymerase inhibitors with HCV eradication rates of >95%.

The eradication of HCV RNA is predicted by the achievement of SVR and defined by the absence of HCV RNA by polymerase chain reaction three to 6 months after stopping treatment. An SVR is associated with a 99% chance of being HCV RNA negative during long-term follow-up and can therefore be considered an indication of a cure of the HCV infection. With the growing availability of highly effective interferon-free regimens for HCV infection, a curative all-oral treatment is becoming a possibility for the vast majority of patients. The second-generation protease inhibitors that have been approved for treatment of HCV and are available in the market are simeprevir, sofosbuvir, ledipasvir/sofosbuvir, daclatasvir, and the combination of ombitasvir-paritaprevir-ritonavir and dasabuvir. Trials are still ongoing on other new products, many of which are expected to appear in the near future.

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8.1. Simeprevir (Olysio®, Janssen Therapeutics)

This is the first available second-generation protease inhibitor (NS3/4A protease inhibitor) indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen [54]. Simeprevir is available in 150 mg capsules to be taken orally once daily with food. The elimination of simeprevir is by the liver, and no dose adjustment is required in the setting of renal impairment [55]. Simeprevir is not recommended in patients with hepatic impairment Child-Pugh Class B and C because of two- to five-fold increases in exposure. In general, simeprevir is well tolerated. Its most common adverse effects are rash (including a potentially serious photosensitivity reaction), pruritus, and nausea. The photosensitivity reaction that related to simeprevir usually occurs during the first 4 weeks of therapy but can develop at any time on treatment. Patients taking simeprevir may experience transient increases in serum bilirubin levels that peak at week 2 of treatment, but these are typically mild in severity and not associated with elevated hepatic aminotransferase levels [56,57]. The coadministration of simeprevir with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended, as this may lead to significantly lower or higher exposure of simeprevir, respectively, which may result in reduced therapeutic effect or adverse reactions. A number of compounds are contraindicated in patients receiving simeprevir, including the following:

1. Antibiotics (erythromycin, clarithromycin, telithromycin, rifampin, rifabutin, rifapentine)
2. Systemically administered antifungals (itroconazole, ketoconazole, voriconazole, posaconazole, fluconazole)
3. Anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)
4. Systemically administered dexamethasone
5. Herbal products (milk thistle, St. John's wort)
6. A number of antiretroviral drugs, including cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir.

Simeprevir is safe in patients using immunosuppressants, such as cyclosporine and tacrolimus, with no dose adjustment, and safe in those using lamivudine, emtricitabine, tenofovir, abacavir, raltegravir, maraviroc, and rilpivirine. The dose of simeprevir needs adjustment with some antiarrhythmics, warfarin, HMG Co-A reductase inhibitors, sedative/anxiolytics, and calcium channel blockers [58-64].

8.2. Sofosbuvir (Sovaldi®, Gilead Sciences)

This is an HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen. Sofosbuvir is available as a 400-mg tablet. The recommended dose of sofosbuvir is 400 mg taken orally once daily, with or without food, regardless of the patient's genotype or prior hepatitis C treatment experience. No dose adjustment is needed for mild-to-moderate renal

impairment or with mild, moderate, or severe hepatic impairment. Currently, no dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate <30 ml/min) or with end-stage renal disease due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. Sofosbuvir has pan-genotypic HCV activity and is effective in treatment-naive, treatment-experienced, and HIV-coinfected patients with compensated cirrhosis, and in patients with hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation. Sofosbuvir has been very well tolerated in clinical trials. The most common adverse effects (≥20%) observed with sofosbuvir, when used in combination with ribavirin, have been fatigue and headaches. The most common adverse events (≥20%) observed in combination with pegylated IFN-α and ribavirin were fatigue, headaches, nausea, insomnia, and anemia. Drugs that are potent P-glycoprotein (P-gp) inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Thus, sofosbuvir should not be administered with other known inducers of P-gp, such as rifampin, carbamazepine, phenytoin or St. John's wort [62,65-77].

8.3. Ledipasvir-sofosbuvir (Harvoni®, Gilead Sciences)

The nucleotide polymerase inhibitor sofosbuvir (400 mg) has been combined with the NS5A inhibitor ledipasvir (90 mg) in a single tablet regimen (SOF/LDV) administered once daily. The combination of ledipasvir-sofosbuvir has primarily been studied as an all-oral (interferon-free) combination regimen in treatment-naive and treatment-experienced patients with genotype 1 chronic HCV infection. For patients with mild to moderate renal impairment, no dosage adjustment of ledipasvir/sofosbuvir is recommended. Severe renal impairment (estimated glomerular filtration rate <30 mL/min) does not substantially affect the pharmacokinetics of ledipasvir, but because levels of sofosbuvir and its metabolite accumulate in the setting of severe renal impairment, the combination should not be used in such settings pending further data. Thus, no dosage recommendation has been given for patients with severe renal impairment or end-stage renal disease requiring dialysis. Available data from clinical trials have shown that the combination of ledipasvir and sofosbuvir has been very well tolerated. The most commonly reported adverse effects are fatigue and headaches. Ledipasvir, like sofosbuvir, is a substrate of the P-gp drug transporter, so drugs that are potent intestinal P-gp inducers may decrease ledipasvir levels. Thus, the coadministration of ledipasvir-sofosbuvir is not recommended with rifampin, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, or tipranavir/ritonavir. In addition, ledipasvir is an inhibitor of P-gp and may increase absorption of P-gp substrates. The coadministration of ledipasvir with tenofovir results in increased levels of tenofovir, particularly in the presence of other boosting agents. Until further data are available, ledipasvir-sofosbuvir should not be used with the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir, and should only be used cautiously with regimens that contain tenofovir and a ritonavir-boosted protease inhibitor [73,78-83].

8.4. Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (Viekira Pak®, AbbVie Inc)

The Viekira Pak is an all-oral regimen comprised of four medications: ombitasvir, paritaprevir, ritonavir, and dasabuvir. This regimen can be used with or without ribavirin. In the Viekira

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Pak, ombitasvir, paritaprevir, and ritonavir (Viekirax®) are combined as a fixed-dose tablet and the dasabuvir (Exviera®) is a separate tablet. Ombitasvir, paritaprevir, and dasabuvir are direct-acting antivirals (DAAs) that directly interfere with HCV replication. Ombitasvir is an NS5A inhibitor with potent pan-genotypic picomolar antiviral activity, paritaprevir is an inhibitor of the NS3/4A serine protease, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. Ritonavir is a CYP3A inhibitor, and it boosts the blood levels of paritaprevir. Paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) are coformulated in a single tablet taken as two tablets once daily. This tablet is combined with dasabuvir (250 mg) taken as one tablet twice daily. The regimen ombitasvir-paritaprevir-ritonavir plus dasabuvir is FDA approved for the treatment of chronic hepatitis C genotype 1, including those with compensated cirrhosis. The regimen ombitasvir-paritaprevir-ritonavir plus dasabuvir, with or without ribavirin, has primarily been studied as an all-oral (interferon-free) regimen in treatment-naive and treatment-experienced patients with genotype 1a or 1b chronic HCV infection, including those with compensated cirrhosis, HIV coinfection, and after receipt of liver transplantation. For patients with mild hepatic impairment (Child-Pugh A), no dosage adjustment is required for ombitasvir-paritaprevir-ritonavir and dasabuvir; however, this regimen is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated with severe hepatic impairment (Child-Pugh C). For patients with mild, moderate, or severe renal insufficiency, no dosing adjustment is required for the regimen ombitasvir-paritaprevir-ritonavir and dasabuvir; this regimen, however, has not been adequately studied in patients with end-stage renal disease on dialysis. Available data from clinical trials have demonstrated excellent tolerance with the ombitasvir-paritaprevir-ritonavir and dasabuvir regimen. The most common (greater than 10%) adverse effects observed in clinical trials when used without ribavirin have been fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. The concomitant use of ombitasvir-paritaprevir-ritonavir and dasabuvir with ethinyl estradiol-containing medications (e.g., oral contraceptives) can result in significant elevations in hepatic aminotransferase levels; accordingly, patients should discontinue any ethinyl estradiol-containing medications prior to starting ombitasvir-paritaprevir-ritonavir and dasabuvir. The use of ombitasvir-paritaprevir-ritonavir plus dasabuvir can potentially cause significant drug-drug interactions, primarily because of the potent ritonavir inhibition of CYP3A4 enzyme. There are a number of medications contraindicated to use concomitantly with ombitasvir-paritaprevir-ritonavir and dasabuvir, like carbamazepine, phenytoin, phenobarbital, gemfibrozil, rifampin, ergotamine, oral contraceptives containing ethinyl estradiol, lovastatin, simvastatin, sildenafil, orally administered midazolam, and St. John's wort. The efficacy of ombitasvir-paritaprevir-ritonavir plus dasabuvir is not known for patients with prior virologic failure and resistance with treatment that included another NS3/4A inhibitor, NS5A inhibitor, or NS5B inhibitor [84-90].

8.5. Daclatasvir (Daklinza®, Bristol-Myers Squibb)

The European Commission approved daclatasvir, a potent pan-genotypic NS5A replication complex inhibitor (in vitro), at the end of August 2014. Daclatasvir should be administered at the dose of 60 mg (one tablet) once per day. It is well tolerated overall. Dose adjustments are not needed in patients with Child B or C disease. Daclatasvir can be used in combination with

other drugs for the treatment of chronic HCV infection genotypes 1, 2, 3, and 4 in adults. Daclatasvir, when used in combination with sofosbuvir, is an all-oral, interferon-free regimen that provided cure rates of more than 95% in clinical trials, including in patients with advanced liver disease, genotype 3, and those who have previously failed treatment with protease inhibitors. Across clinical studies, daclatasvir-based regimens have been generally well tolerated, with low discontinuation rates. The most common adverse effects with daclatasvir when used in combination with other drugs are fatigue, headaches, and nausea. Little information has been released on daclatasvir drug-drug interactions. Daclatasvir is a substrate of CYP34A and a substrate and inhibitor of P-gp. The daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz. No dose adjustment is needed with tenofovir. No information on other antiretroviral drugs is available yet. No dose adjustments are required with cyclosporine or tacrolimus. Total daclatasvir AUC is decreased by 40% and 43% in patients with mild or moderate liver impairment, respectively. However, the unbound pharmacologically active fraction is unchanged; thus, dose adjustment is not needed in patients with liver impairment [77,91,92].

The direct acting antiviral treatment is usually used in combination for HCV treatment according to genotypes and stage of liver disease, and the patient is either naive or has previous experience of treatment.

The following recommendations can be used for treatment of HCV according to genotypes with a high response rate (>90%):

1. HCV genotype 1 [91,93]

a. Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis. The duration of treatment extended to 24 weeks in patients with contraindications to ribavirin.

b. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) for treatment of both naive and prior pegylated interferon and ribavirin treatment failure, in patients with HCV genotype 1a infection.

c. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks for treatment-naive and prior pegylated interferon and ribavirin treatment failure, in patients with HCV genotype 1b infection. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis.

d. Daily fixed-dose combination of daclatasvir 60 mg and sofosbuvir 400 mg for 12 weeks. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis. The duration of treatment extended to 24 weeks in patients with contraindications to ribavirin.

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e. Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis. The duration of treatment extended to 24 weeks in patients with contraindications to ribavirin.

f. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly pegylated interferon for 12 weeks.

2. HCV genotype 2 [91,93]

a. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks; extending duration of treatment to 16-20 weeks is recommended in patients with cirrhosis and those in whom prior pegylated interferon and ribavirin treatment has failed.

b. Daily sofosbuvir (400 mg) and daclatasvir (60 mg) for 12 weeks in cirrhotic or treatment-experienced patients.

c. Retreatment with daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) plus weekly pegylated interferon for 12 weeks is an alternative in patients where prior pegylated interferon and ribavirin treatment has failed.

3. HCV genotype 3

When pegylated interferon and ribavirin was the treatment for HCV, the same regimen was administered to all subjects, and patients were defined as easy or difficult to treat according to viral genotype. HCV genotypes 1 and 4 were considered to be difficult to treat, and HCV genotypes 2 and 3 were considered to be easy to treat. The SVR rates in the latter group were above 80% with shorter treatment [94,95]. The availability of interferon-free regimens has confirmed that HCV genotype 2 patients are easy to treat, while the paradigm for HCV genotype 3 patients has been reversed compared to "older, difficult-to-treat" HCV genotype 1 patients. In fact, today, with available direct acting antiviral drugs, patients with HCV genotype 3 are the most difficult to treat patients. In large studies on HCV genotype 3 to assess the effectiveness of 12-16 weeks treatment with sofosbuvir and ribavirin, it has been shown that 12 weeks of therapy in treatment-naive patients resulted in an SVR in 61% and 34% of noncirrhotic and cirrhotic patients, respectively. Moreover, the SVR rates in experienced noncirrhotic patients were 37% at 12 weeks and were increased to 63% in patients with 16 weeks' course [70,67,95]. Extended treatments to 24 weeks of sofosbuvir and ribavirin were evaluated in the valence trial, resulting in an overall SVR rate of 83%. In particular, this was the result of higher SVR rates in treatment-naive (93% and 92% in patients without and with cirrhosis, respectively) and experienced patients without cirrhosis (87%), while rates were lower in experienced (61%) patients with cirrhosis [80,95,96]. The Lonestar-2 study tested treatment with pegylated interferon/sofosbuvir/ribavirin for 12 weeks in treatment-experienced HCV-2 and HCV-3 patients. The SVR in HCV genotype 3 patients was 83% with no difference in relation to baseline cirrhosis (SVR 83% vs. 83%, respectively) [69]. The second study tested a combination of daclatasvir/sofosbuvir, resulting in an SVR of 89% of 18 treatment-naive patients with HCV genotype 3 [97].

The following treatment options with similar efficacy can be used in genotype 3 naive patients and patients in whom prior pegylated interferon and ribavirin treatment has failed [91-93,97]:

a. Daily fixed-dose combination of daclatasvir 60 mg and sofosbuvir 400 mg for 12 weeks in patients without cirrhosis. Daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is added to regimen to treat naive and treatment-experienced patients with cirrhosis for 24 weeks.

b. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks.

c. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly pegylated interferon for 12 weeks is an acceptable regimen for interferon-eligible, treatment-naive patients with HCV genotype 3 infection.

4. HCV genotype 4 [70,91,93,98-101]

a. Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis. The duration of treatment extended to 24 weeks in patients with contraindications to ribavirin.

b. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks for treatment of both naive and prior pegylated interferon and ribavirin treatment failure, and treatment can be extended to 24 weeks in patients with cirrhosis.

c. Daily fixed-dose combination of daclatasvir 60 mg and sofosbuvir 400 mg for 12 weeks. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis. The duration of treatment extended to 24 weeks in patients with contraindications to ribavirin.

d. Daily sofosbuvir (400 mg) plus simeprevir (150 mg) for 12 weeks. The addition of daily weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) is recommended in patients with cirrhosis. The duration of treatment extended to 24 weeks in patients with contraindications to ribavirin.

e. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly pegylated interferon for 12 weeks.

5. HCV genotype 5 [91,93]

A few data are available to help guide decision making for patients infected with HCV genotype 5 or 6, but currently the following are the recommendations until more data are available:

a. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly pegylated interferon for 12 weeks

b. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks

c. Weekly pegylated interferon plus weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 48 weeks is an alternative regimen for interferon-eligible, treatment-naive patients.

6. Genotype 6 [91,93]

a. Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks

b. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) plus weekly pegylated interferon for 12 weeks

c. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks

Due to the very high efficacy and the excellent tolerability of IFN-free regimens, response-guided shortening or prolongation of therapy have not been studied and, indeed, may not be needed to achieve high cure chances in the individual patient. However, given the high costs of direct antiviral drugs, HCV RNA testing during treatment may be helpful for surveillance of compliance and motivation of patients. HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy [102].

9. Treatment of special populations with direct acting antiviral regimens

9.1. HIV/HCV-coinfected individuals

Hepatitis C virus (HCV)-related liver disease is a major source of mortality in HIV-infected patients. Approximately one third of all patients with HIV are coinfected with HCV. Patients coinfected with HIV/HCV have shown lower rates of SVR with pegylated-interferon and weight-based ribavirin as well as more rapid progression of fibrosis than those with HCV monoinfection [103]. HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications. Based on AASLD/IDSA/IAS-USA [93], the following precautions should be considered:

a. Antiretroviral treatment interruption in patients with HIV/HCV is not recommended to allow HCV therapy.

b. Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) should not be used with cobicistat and elvitegravir, pending further data.

c. Sofosbuvir or ledipasvir/sofosbuvir should not be used with tipranavir because of the potential of this antiretroviral drug to induce P-gp.

d. Fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) should not be used with efavirenz, rilpivirine, darunavir, or ritonavir-boosted lopinavir.

e. Paritaprevir/ritonavir/ombitasvir with or without dasabuvir should not be used in HIV/HCV-coinfected individuals who are not taking antiretroviral therapy.

f. Simeprevir should not be used with efavirenz, etravirine, nevirapine, cobicistat, or any HIV protease inhibitors.

g. Ribavirin should not be used with didanosine, stavudine, or zidovudine.

The management of HIV/HCV patients should take place in collaboration with an HIV practitioner. Special precautions should be taken when prescribing DAAs in patient on AIDS treatment to avoid under- or overdose in such patients as a result of drug-drug interactions. For example, ledipasvir increases tenofovir levels, concomitant use needs to be avoided in patients with CrCl below 60 mL/min. Because potentiation of this effect is expected when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination. Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which it does not have substantial interactions like atazanavir, enfuvirtide, lamivudine, emtricitabine, tenofovir, and raltegravir (and probably dolutegravir) [93].

The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir, and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination. Simeprevir should only be used with antiretroviral drugs, with which it does not have clinically significant interactions like raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, and abacavir [93].

9.2. Patients with decompensated cirrhosis

In patients with Child-Pugh B or C cirrhosis awaiting transplantation, antiviral therapy may be offered on an individual basis in experienced centers, pending the presentation of more data in this population. It is possible that patients with decompensated cirrhosis who are not on a transplant list could benefit from an interferon-free treatment regimen. However, the safety and efficacy of an interferon-free regimen in patients with decompensated cirrhosis not on a transplant waiting list is unknown, and the impact on mortality in this group is not yet established. According to AASLD/IDSA/IAS-USA [93] and EASL recommendations on treatment of hepatitis C 2015 [91], the following medications can be used with high virological response >90%:

a. Decompensated cirrhosis: genotypes 1 and 4

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) and ribavirin (initial dose of 600 mg, increased as tolerated) for 12 weeks is recommended for patients with decompensated cirrhosis.

- For patients with decompensated cirrhosis and anemia or ribavirin intolerance, daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is recommended.
- For patients with decompensated cirrhosis in whom prior sofosbuvir-based treatment has failed, daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) and ribavirin (initial dose of 600 mg, increased as tolerated) for 24 weeks is an alternative regimen.
- Daily fixed-dose combination of sofosbuvir (400 mg), ribavirin (initial dose of 600 mg, increased as tolerated), and daclatasvir 60 mg for 12 weeks before liver transplantation is recommended for patients with decompensated cirrhosis.

b. Decompensated cirrhosis: genotypes 2 and 3

- Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) (doses need to be adjusted according to the patient's creatinine clearance rate and hemoglobin level) for up to 48 weeks is recommended for patients with HCV genotype 2 or 3 who have decompensated cirrhosis.

9.3. Patients with HCV recurrence post liver transplantation

Patients with posttransplant recurrence of HCV infection should be considered for therapy. Significant fibrosis or portal hypertension 1 year after transplantation could predict rapid disease progression and graft loss and could indicate the need for more urgent antiviral treatment. Interferon-free DAA can cure most liver transplant recipients with recurrent hepatitis C, including a majority of those with severe post-transplant liver disease. In addition to viral suppression, treatment also improves liver function. DAA treatment is generally safe and well tolerated, certainly more so than interferon-based therapy, although anemia remains a concern for people taking ribavirin. Drug-drug interactions may be important in the posttransplant setting. No clinically significant drug-drug interactions have been found between sofosbuvir, simeprevir, or daclatasvir on the one hand, and cyclosporine and tacrolimus on the other hand.

The following options proved to be useful in post-liver transplantation patients according to genotypes, with high virological response, waiting more data in near future [91,93,104,105]:

a. Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 weeks is recommended for patients with HCV genotype 1 or 4 infection in the allograft, including compensated cirrhosis.

b. Patients who are ribavirin intolerant or ineligible, ledipasvir (90 mg)/sofosbuvir (400 mg) usually extended for 24 weeks in patients with HCV genotype 1 or 4 infection.

c. Daily sofosbuvir (400 mg) plus simeprevir (150 mg) with or without weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 12 to 24 weeks in patients with genotype 1 or 4 infection in the allograft, including compensated cirrhosis.

d. Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 mg]), in the allograft, without cirrhosis, for 24 weeks in patients with HCV genotype 1 infection.

e. Daily sofosbuvir (400 mg) plus daclatasvir (60 mg) with or without weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks for patients with HCV genotypes 1, 3, 4, 5, and 6 in the allograft, including those with compensated and decompensated cirrhosis is another combination with high virological response and improvement of liver function.

f. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is recommended for patients with HCV genotype 2 in the allograft, including compensated cirrhosis.

g. Daily sofosbuvir (400 mg) and weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [>75 kg]) for 24 weeks is recommended as alternative for treatment patients with HCV genotype 3 infection in the allograft, including compensated and decompensated cirrhosis.

9.4. Patients with renal impairments

For patients with creatinine clearance of >30 mL/min, no dosage adjustment is required when using simeprevir, sofosbuvir, daclatasvir, fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg), or fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) to treat patients with HCV infection. Simeprevir, daclatasvir, and the combination of paritaprevir, ritonavir, ombitasvir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal impairment [91].

EASL Recommendations on Treatment of Hepatitis C 2015 and AASLD/IDSA/IAS-USA 2014 guidelines on HCV treatment do not recommend sofosbuvir in patients with creatinine clearance of <30 mL/min or with ESRD until more data are available [91,93].

9.5. Patients with acute HCV infection

When the efficacy of the treatment of acute HCV infection was superior to the treatment of chronic infection, there was a strong impetus to identify and treat acute HCV infection with interferon [106]. The current availability of interferon-sparing HCV treatments that have high safety and efficacy reduces the advantage of early treatment of HCV infection. Until data documenting the efficacy and safety of treatment of acute hepatitis C with direct acting antiviral drugs are available, monitoring for spontaneous clearance for minimum of 6 months before initiating treatment is required. When a decision is made to treat patients after 6 months of acute infection, then the patient can be treated as described for chronic HCV [93].

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10. Conclusion

Chronic hepatitis C in the presence of the new direct-acting antiviral drugs became a curable disease, with a sustained virological response of more than 90%. The second-generation protease inhibitors that have been approved for treatment of HCV and are available in the market are simeprevir, sofosbuvir, ledipasvir/sofosbuvir, daclatasvir, and the combination of ombitasvir-paritaprevir-ritonavir and dasabuvir. The cost of these new agents prevents universal delivery of medications and prioritization of treatment should be given to patients who are in need of immediate care like those with advanced liver disease and extrahepatic complications. Trials are still ongoing with other new products, many of which are expected to appear in the market soon.

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