We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 1

Introductory Chapter: Current and Emerging Anti-Hepatitis C Regimens: Hope or Hype

Imran Shahid

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.81237

1. Introduction

1.1. Hepatitis C is curable now

Since its discovery in 1989, hepatitis C virus (HCV) infection always remained a big challenge for the physicians, clinicians, and healthcare providers to treat as well as for the scientists and researchers to design and develop novel compounds to inhibit viral replication and polyprotein processing. The classical treatment by interferon therapy as once known as the "gold standard of care" was not so much effective in different HCV genotype (GT)-treated patients, and treatment-emergent adverse events were generally a potential reason of treatment discontinuation [1]. The addition of ribavirin (RBV) to pegylated interferon (PEG-IFN) raised the hopes to achieve high cure rates; however, dual therapy was successful 70–80% in HCV GT 3 and only 50–60% in HCV GT 1- and GT 2-infected patients. In that era, the ample understanding of HCV life cycle, better understanding of pathophysiology of the disease, and the emergence of new technologies urged the researchers to develop novel compounds which directly target to different parts of the HCV genome which are essential components of viral replication and polyprotein processing [1].

1.2. Novel treatment options on the horizon

The landscape in hepatitis C medicine started to revolutionize from 2011, when the first time direct-acting antivirals (DAAs) were administered to hepatitis C virus-infected patients along with PEG-IFN and RBV [1]. After that, the advent and approval of different DAA combination have shifted the treatment paradigms for all seven HCV GT-infected patients and even difficult-to-treat-specific populations (HCV GT 1a- and GT 3-infected

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

individuals, cirrhotic patients, HCV/HIV coinfection, severe renal impairment and liver transplant, and previous treatment failure with NS3/4A or NS5A inhibitors). By inhibiting viral replication and blocking polyprotein processing, these novel and innovative DAAs are categorized into four groups, namely, nucleoside RNA-dependent RNA polymerase (RdRp; NS5B protein) inhibitors (NIs), non-nucleoside RdRp inhibitors (NNIs), viral replication complex inhibitors (i.e., NS5A protein), and viral serine protease (i.e., NS3/4A protein) inhibitors (PIs) [1]. Interestingly, the treatment regimens achieve higher sustained virologic response rates (SVR; HCV viral RNA undetectable at the end of week 12) only when used in combination as dual or triple therapeutic regimens, and single DAA therapy is either not so much effective or recommended to use [2]. Some DAAs have been developed as a single pill of fixed dose combination (FDC) of two, three, or even more compounds, and all DAAs are given orally to infected patients. The use of RBV is still considered an integral part of some DAAs while considering certain complicated hepatitis C patient populations including HCV cirrhotic patients; treatment-experienced patients with PEG-IFN, PEG-IFN/RBV, and first-generation PIs (telaprevir, boceprevir); and patients with decompensated cirrhosis. In parallel to that, the treatment strategies, dosage frequencies, and treatment duration vary for different HCV GTs and harder-to-treat-specific patient populations (e.g., HCV GT 3-infected patients; HCV patients with compensated/decompensated cirrhosis; previous treatment failure with PEG-IFN/RBV, first-generation PIs, and NS5A inhibitors; HCV/HIV coinfection; and patient with liver transplant or severe renal impairment). Some treatment options with pan-genotypic HCV coverage have been approved by the Food and Drug Administration (FDA) of the United States of America (USA), and some are in the final stage of development. Some different antivirals with an alternate mechanism of action such as by inhibiting viral entry or cell-to-cell spread and some anti-mRNA-based strategies like microRNAs are also in the pipeline [1, 2].

1.3. The treatment for hepatitis C is remarkably effective but with caveat

The clinicians, seeing outcomes they never thought possible, and experts are optimistic that more complex and challenging patients will respond to therapy. It has amalgamated the efforts to purge the viral scourges, to cure the infection, and to accomplish the potential global goal of HCV eradication. However, treatment choices can be tricky, and caveats are emerging including the recurrence of liver cancer and hepatitis B reactivation in chronically infected HCV or difficult-to-treat individuals. Equivocally, several important issues prevail linking to disease prevalence, viral screening, therapy adherence, reinfection, drug costs, expansion of care domain, and emergence of resistance-associated substitutions (RASs) in hepatitis C populations. Despite the incredible evolution in HCV therapeutics, much remains to be done to the point where it is a minimal entity. Now is the provident time to carefully consider population-level priorities and engineer HCV treatment strategies along with health policies which are realistic vis-à-vis implementation at a national or even pan-national level.

This book intends to comprehensively discuss hepatitis C virus infection progression, associated HCV clinical implications, and revolutionary anti-hepatitis C regimens and lends crucial insights on the opportunities that new therapies will bring to eliminate this silent but curable disease. It is not possible to discuss here HCV pathophysiology and therapeutics in detail,

but our intentions and aims in the introductory book chapter (Chapter 1) and the whole book itself are very clear: to provide general but valuable information from a common reader to an HCV specialist as well as to sketch a complete landscape of hepatitis C from infection to cure.

2. HCV disease progression

Afflicting around 170 million people worldwide [1], HCV infection is the foremost cause of liver cirrhosis, liver fibrosis, and hepatocellular carcinoma (HCC) and the first reason for liver transplantation [3]. The propagation of hepatitis C from acute to chronic infection and afterward to end-stage liver diseases involves a highly orchestrated series of molecular and cellular events including a plethora of genes and cell signaling cascades. The acute phase of infection is frequently asymptomatic or associated with mild and nonspecific symptoms. Persistent HCV infection is one of the major causes of chronic liver disease in 80% of infected individuals [4]. Approximately 20% of chronic carriers may develop liver cirrhosis, and some of these cases will progress to hepatocellular carcinoma (HCC). Consequently, HCV-induced chronic liver disease is recognized as the leading indication for orthotopic liver transplantation [5]. The studies demonstrate that HCV-induced inflammatory responses use host responses to recruit inflammatory cells and further prime a coordinated event of several host protein-protein interactions [4, 5]. Chapter 2 of this book highlights the recent advances in HCV-induced inflammatory responses and the role of inflammation during HCV infection. In addition, HCV affects other body cells including the immune system cells, and this ability of HCV to disrupt immune cells is evident to cause occult infection (e.g., mixed cryoglobulinemia and B-cell non-Hodgkin's lymphoma) [6]. How HCV lymphotropism affects the function of immune cells, virus persistence, and immune cell proliferation are discussed in Chapter 3. It is also believed that the progression of HCV to hepatocellular carcinoma (HCC) involved DNA methylation of cancer-related genes [7]. Chapter 4 illustrates how the detection of such genes may be helpful to know the different stages of disease progression from hepatitis C to HCC. In the setting of HCV infection, the role of various microRNAs (miRNAs) in modulating viral infection response has been deeply studied that clarifies causes of chronic hepatitis C progression in most infected patients and consequences of infection with manipulation in the risk of developing HCV-related comorbidities (i.e., cirrhosis and hepatocellular carcinoma) [8]. miRNAs are a class of small, endogenous, conserved, noncoding RNAs with a length of 20–24 nucleotides which posttranscriptionally regulate target genes. miRNA are also proved as key regulators of homeostasis for multiple biological systems, besides modulation of the disease pathology of many cancers. Similarly, miRNAs act as key modulators of HCV and hepatitis B virus (HBV) infection and liver disease progression [8]. Chapter 5 elaborates the regulation of miRNAs in HCC-related HCV patients.

3. HCV-associated clinical implications

Metabolic syndrome, obesity, and insulin resistance are very common health problems around the world with an increased morbidity rate. These comorbidities further contribute to hepatic steatosis, which ultimately lead to fat deposition in the liver [9]. Some studies predict that

these pathological states may limit response to IFN-based treatment regimens while treating hepatitis C; however, interestingly therapeutic response is not impaired to DAAs [10]. Now with curative treatment options available for patients with HCV, the sequelae of steatosis, fibrosis, and its drivers will garner more attention. Several other metabolic factors (e.g., vitamin D) could be related to more liver damage and high degree of fibrosis [9, 10]. In Chapter 6, Prof. Villar reviews the challenges and metabolic pathology associated with HCV infection and highlights some metabolic factors with their significant impact on liver damage. Several studies demonstrate that HCV infects other body organs and clinical implications may be very serious in chronically infected HCV patients. Some clinical studies suggest the association of HCV for the onset of periodontal disease in infected individuals [11]. The connection such connections between periodontal disease and hepatitis C must be considered by relevant healthcare practitioners due to their important implications on clinical manifestations and treatment strategies. Prof. Surlin Petra describes an update on periodontal implication of hepatitis C infection in Chapter 7. In addition to that, epigenetic modulation during HCV infection progression may also contribute to the development of HCV-related liver diseases (e.g., hepatic fibrosis and hepatocarcinogenesis) [12]. Chapter 8 describes the host and viral factors associated with the progression of hepatic fibrosis in HCV-infected individuals.

4. Current treatment landscape

4.1. The new HCV drugs are considered revolutionary

Treatment of chronic hepatitis C has markedly been improved with the introduction of IFN-free DAA therapies since 2011. New DAAs for chronic hepatitis C can cure infection in more than 95% of patients. Greater provision of DAAs, as well as greater efficacy of these medications in recent years, has led to a steady increase in SVR rates in HCV patients. The big picture is one of the clinical successes where we know that 95–100% of patients treated for hepatitis C can be cured [13]. It is pretty amazing.

The currently available DAAs are based on their target site with a particular mechanism of action [1, 2, 13]. NS3-4A serine protease inhibitors (NS3-4A PIs) block posttranslational processing of viral polyproteins by binding to the catalytic site of the enzyme which prevent the release of functional, nonstructural proteins. The first-generation PIs (i.e., telaprevir and boceprevir) were recommended for HCV GT 1-infected patients in 2011 in combination with PEG-IFN and RBV as a triple regimen with estimated SVR rates between 65 and 80%. However, the treatment-emergent adverse events, potential drug-drug interactions, essential necessity of PEG-IFN, and low genetic barrier to drug resistance were the major disadvantages associated with these drugs. Consequently these regimens are not recommended to treat hepatitis C and were discontinued. The landmark era in HCV therapeutics was started in December 2013 when the first IFN-free all-oral regimen, an NI inhibitor (sofosbuvir) also known as "Magic bullet," was approved for hepatitis C treatment [13]. The SVR rates achieved were more than 90%, and the regimen was considered safe, with fewer drug-drug interactions, very low adverse event profile, superior SVR rates, and an ability to use in combination with other regimens to treat difficult HCV populations with satisfactory therapeutic outcomes. After that a

series of innovative DAAs have been approved by the US FDA to treat hepatitis C with excellent SVR rates. The second-generation DAAs in combination are highly effective to treat the wide spectrum of HCV populations, and some have shown clinical promise as pan-genotypic and panfibrotypic coverages [2, 13]. The first-generation PIs include telaprevir (TVR) and boceprevir (BOC), while second-generation PIs include simeprevir (SMV), ritonavir-boosted paritaprevir (PTV), asunaprevir (ASV), grazoprevir (GZR), voxilaprevir (VOX), and glecaprevir (GLE). NS5A inhibitors block their regulation capability of viral replication within the replication complex and also inhibit the viral assembly and release. First-generation NS5A inhibitors include daclatasvir (DCV), ledipasvir (LDV), ombitasvir (OBV), and elbasvir (EBR), while velpatasvir (VEL) and pibrentasvir (PIB) are categorized into second- or next-generation NS5A inhibitors. NNIs bind to one of the four allosteric sites of RdRp and block the catalytic function of RdRp which indirectly block RNA replication. Dasabuvir (DSV) is the only FDA-approved NNI, which is used in combination with other DAAs to treat hepatitis C. NIs act as a false substrate for HCV RNA polymerase enzyme during viral replication where its incorporation results in chain termination during viral RNA synthesis. Sofosbuvir (SOF) is the sole example in this category of IFN-free DAA regimens. However, SOF sets a new standard of care for HCV patients as it is used in combination with other DAAs for the treatment of almost all HCV GT patients and even difficult-to-treat-specific populations [1, 2, 13].

4.2. Pan-genotypic regimens

Until now, the US FDA has approved three pan-genotypic DAA combination regimens to treat HCV GT 1–6 and even difficult-to-treat-specific populations. The first pan-genotypic combination regimen including SOF and VEL (*Epclusa*®) as a FDC of single pill for 12 weeks is recommended for GT 1–6 patients without cirrhosis or with compensated cirrhosis. The regimen is also administered to patients with decompensated cirrhosis; however, in this case RBV is added to active regimens [2]. In July 2017, the US FDA approved *Vosevi*® (SOF/VEL/VOX) to treat adults with chronic hepatitis C GT 1 to 6 without cirrhosis or with mild cirrhosis [14]. *Vosevi*® is a once-daily single tablet that contains two previously approved drugs—the NIs SOF (400 mg) and NS5A inhibitor VEL (100 mg)—and the newly approved pan-genotypic PIs VOX (100 mg). *Vosevi*® is the first FDA-approved treatment for patients who have been previously treated with the DAAs SOF or other drugs for HCV that inhibit NS5A. SVR12 was achieved in more than 90% of patients after the end of treatment [14]. In August 2017, the US FDA approved the combination of GLE and PIB (*Maviret*®) for the treatment of chronic hepatitis C for adults with chronic HCV GT 1 to 6 without cirrhosis or with mild cirrhosis including those with moderate to severe kidney disease and those on dialysis [15]. It is also indicated for adults infected with HCV GT 1 who were previously treated with either an NS5A inhibitor or an NS3/4A PIs, but not both. The drug reduces by 4 weeks the time needed for a cure by administering once daily as three oral tablets. The treatment regimen for GLE/PIB lasts 8 weeks, while the standard treatment length previously was at least 12 weeks for other DAA combinations. The combination GLE/PIB is also effective for treating HCV infection in individuals coinfected with HIV-1, according to results from the non-randomized, open-label phase III clinical trials [16]. Both *Vosevi*® and *Maviret*® are active against all HCV GTs, and with little differences, the two medicines may be specifically useful in some harder-to-treat-specific populations or those who failed or cannot use previously available therapies

[14–16]. In Chapter 9, Prof. Sidra discusses the safety, tolerability, and associated side effects of DAAs emphasizing their clinical pharmacology as well as the important safety issues of drug-drug interactions (DDIs). Similarly, Prof. Tran in Chapter 10 overviews a mathematical model while using sensitivity and identifiability techniques to determine model parameters in hepatitis C viral dynamics using a combination therapy of IFN, RBV, and TVR for partial viral response, sustained viral response, and breakthrough patients.

4.3. Emerging anti-HCV regimens

An 8-week regimen containing grazoprevir-ruzasvir-uprifosbuvir appears to be effective for treating hepatitis C virus infection in patients with or without cirrhosis, according to findings from a pair of randomized phase II open-label trials [17]. SVR12 rates with 8 weeks of therapy were 93% in individuals with GT 1a, 98% with GT 1b, 86% with GT 2 (without cirrhosis, patients with HCV GT 2 and cirrhosis received a longer course), 95% with GT 3 (treatment naive, without cirrhosis), and 100% with GT 4 and 6. Interestingly, the 8-week duration of therapy for HCV GT 2 patients achieved lower cure rates; however, treatment extension to 12 weeks overcame this effect. The excellent treatment outcomes in phase II clinical trials support further investigation of grazoprevir, ruzasvir, and uprifosbuvir as a pan-genotypic regimen in phase III clinical trials, where this combination has the potential to provide a safe, single-duration regimen for HCV patients with and without cirrhosis including harder-to-treat GT 3 individuals who had previously treated with PEG-IFN and RBV. The clinicians are also hopeful that excellent therapeutic outcomes of such regimens in ongoing phase III clinical trials will provide safer options with regard to pan-genotypic regimens for the treatment of hepatitis C and may impact the current treatment landscape [17].

5. Challenges for new regimens

The advancement in HCV therapeutics is fabulous and trustworthy after the introduction of well-tolerated and safe oral interferon-free DAAs in treatment strategies which provides compassionate treatment for HCV-infected patients to get cured and back to normal life. However, the next frontiers in front of researchers and clinicians are to coup certain challenges which may interrupt to achieve high cure rates in treated individuals and may be a potential cause of suboptimal SVR rates in difficult-to-treat subpopulations in real-world clinical practice. Until now, the real-world clinical data is not so much largely published/produced to make a clear understanding and interpretation of these obstacles; however, the treatment costs, risks of HBV reactivation and liver cancer recurrence, and the emergence of resistance-associated substitutions (RAS) are potential barriers which may prevent to achieve the global goal of HCV eradication [2]. Likewise, the dosage algorithms and safety profiles of such regimens in patients under age 18, in pregnant females, and end-stage liver disease and post-transplant patients are yet to be extensively elucidated [2]. The following section briefly overviews these harboring issues with some supporting clinically published data and also suggests some possible solutions in this prospect.

5.1. Drug costs and treatment access

The high therapy cost in the developing world or even in resource-replete nations and lack of treatment access in some areas where HCV is highly prevalent (e.g., in Egypt and some part of South Asia, where HCV is endemic) are major limitations of current anti-hepatitis C regimens [2]. An average treatment cost may be from 65,000 to 110,000 USD when brand-name therapies are administered to HCV-infected patients for a 12-week duration. Is it splurging at these prices to cure hepatitis C? The answer is certainly no. In the USA, most of the insurance companies have adopted a policy of "prioritizing coverage to those who need it the most," and some states are authorizing the treatment while using the extent of a patient's hepatic fibrosis (stage 3 or 4) or cirrhosis to cover the cost of HCV drugs. In some states, the decision is usually left to third-party payers. In Europe, the healthcare policy frequently bases the administration of hepatitis C therapy on fibrosis stage, so the patients with later-stage disease are often given preference. Although the use of HCV generics cut the cost as first data are encouraging in clinical studies, it is too early to comment on the clinical efficacy of these regimens, and the emergence of adverse events in treated individuals is not fully elucidated, and studies are going on. The brand-name drugs are comparatively cheaper in Europe than in the USA but still much expensive in India. The generic drug costs should be even lower to provide these regimens to individuals who need it the most. Such treatment with minimal diagnostic support is urgently required in low- and middle-income countries (12 out of 20 countries with the highest ratio of HCV prevalence are classified as low or lower-middle income) where treatment access is extremely limited due to high drug costs and complexity of patient management. In such areas, "test-and-treat strategies" and "risk-stratified approach" could be implicated to provide a targeted therapy for patients with high risks of HCV progression. In this context, risk prediction tools may help the physicians and patients to decide whether to initiate the treatment with costly DAAs or to sustain affordable treatment even with PEG-IFN and RBV to achieve high SVR rates [2].

5.2. HBV reactivation risk with DAAs

Patients with a past or current HBV infection can experience sometimes fatal HBV reactivation if they take any of 11 approved DAAs for hepatitis C virus (HCV) infection treatment [18]. The US FDA recommends a box warning for the drugs advising clinicians to screen patients for evidence of a past or current HBV infection before ordering antiviral treatment for HCV. The FDA identified 24 cases of HBV reactivation in coinfected patients treated with these antivirals from November 22, 2013, to July 18, 2016, in reports to the agency and published literature. Two patients died, and one needed a liver transplant. Interestingly, clinical trials for the HCV drugs in question/approval did not report HBV reactivation because they excluded patients infected with HBV and it was not reported as an adverse event in phase III clinical trials for the DAAs' approval. Similarly, such exclusion characterizes higher DAA safety, in terms of potential liver adverse reactions in the presence of one virus infection (i.e., HCV) instead of conducting more complicated safety evaluation of DAAs in patients infected with both HBV and HCV. The exact mechanism of HBV reactivation is still not known; however, it is considered that it may result from a complex interplay of host immunologic responses in the setting of infection with two hepatitis viruses. It is also assumed that HBV reactivation

may result from HCV clearance rather than a drug-specific toxicity. The treatment-induced reduction in HCV by DAAs also suppresses HBV, and the lack of activity against HBV of DAAs plus immunologic responses may escape HBV to reactivate [18].

Flare-ups of inactive or once-resolved HBV with DAAs have rung alarm bells before. In March 2016, the European Medicines Agency (EMA) announced that it had launched a review of six DAAs for HCV on the basis of reports of HBV reactivation in individuals infected with both viruses and who were treated with DAAs for HCV [19]. The Pharmacovigilance Risk Assessment Committee (PRAC) review covered six DAAs marketed in Europe for treatment of chronic HCV infection: daclatasvir (*Daklinza*®), dasabuvir (*Exviera*®), the combination of SOF and LDV (*Harvoni*®), simeprevir (*Olysio*®), sofosbuvir (*Sovaldi*®), and the combination OBV/PTV/r (*Viekirax*®). Since the start of this review, two other DAAs, the combination SOF and VEL (*Epclusa*®) and the combination EBR and GZR (*Zepatier*®), have been authorized in the European Union. In December 2016, the PRAC has confirmed the risk for hepatitis B virus (HBV) reactivation when DAAs are used for treatment of HCV infection. The PRAC recommends that, before starting treatment, all patients should be screened for HBV; patients found to be coinfected with HCV and HBV should be monitored and managed according to current clinical guidelines. Although the frequency of HBV reactivation appears low, the PRAC recommends that a warning be included in the prescribing information for these medicines [19].

In September 2016, the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) issued updated guidelines that advise clinicians not to prescribe DAAs to patients with HCV until the patients are screened for HBV, all because the societies were hearing about HBV reactivation in coinfected patients treated with the drugs. If patients who test positive for HBV warrant treatment, they should begin that treatment before or at the same time they start to receive direct-acting antivirals for HCV, according to the guidelines.

5.3. DAAs and cancer risk

5.3.1. Evidence pointing to a heightened cancer risk

DAAs do not appear to increase risk for liver cancer in patients with hepatitis C infection and cirrhosis, but the drugs could make existing but previously undetected cancers worse and harder to treat, according to results from a large-scale prospective study [20]. An interesting but unexpected finding of this study depicted that 50% of the individuals who developed a tumor early in the course of treatment or just after stopping treatment developed a more aggressive type of tumor than what was usually seen in the course of the disease. The researchers hypothesized that HCV replication is halted by DAAs; there are dramatic changes in the immunologic and molecular microenvironment in the liver and in tumor suppression mechanisms, which could allow or even promote the growth of previously undiagnosed microscopic HCC foci. Therefore, it is mandatory that patients treated with DAAs with advanced liver disease continue to be monitored for HCC. The findings also point to the need for careful pretreatment screening and continued monitoring of patients treated with direct-acting antivirals for hepatitis C in particular who have advanced fibrosis and are therefore at risk for liver cancer [20].

An Israeli study also points to an increased risk for malignancy in hepatitis C patients treated with DAAs [20]. Findings from the retrospective assessment of 273 consecutive patients infected with hepatitis C, some with a history of liver cancer and others without, were also reported. A sustained viral response at 12 weeks was achieved by 95% of the patients. However, over the next 15 months, 14 patients, or 5% of all participants, developed malignancy. Specifically, there were six cases of de novo HCC, three cases of recurrent HCC, four cases of extrahepatic cancer, and one case of intrahepatic cholangiocarcinoma. This study also correlates an association between DAA efficacy and malignancies progression with higher risk although the exact mechanism of this association is not known. However, the researchers assumed that the sudden impairment of the immune system may allow the growth of existing preclinical cancer clones [20].

5.3.2. Studies finding no elevated cancer risk

In contrast, investigators saw no increased risk for HCC in patients treated with DAAs in a retrospective study of 178 patients with hepatitis C infection and HCC who were candidates for liver transplantation [21]. The research showed that the cumulative incidence of recurrence over 1 year was lower in patients treated with DAAs before a diagnosis of HCC than in a control group of patients never treated with DAAs. However, when the antivirals were administered after a diagnosis of liver cancer, the risk for recurrence was similar in the antiviral and control groups, which suggests that prediagnosis antiviral therapy could be protective. However, this study was conducted in a different population—liver transplant patients on a wait list, where a statistically significant decrease in HCC recurrence (P = .04) was noticed when patients were administered with DAAs before a HCC diagnosis. When patients had a complete initial response to cancer therapy, DAA use did not significantly increase the transplantation wait-list dropout rate. The study results support the use of DAAs in patients on the transplant wait list with HCC who have achieved initial response to locoregional treatment [21].

A systemic review, meta-analyses, and meta-regression revealed no difference in the risk for HCC in patients treated with DAAs and those treated with IFN-based therapy [21]. This study conducted in Australia, involving 13,875 people from 26 studies on HCC occurrence and 15 studies on disease recurrence, explicited other culprits involved in recurrence of HCC following DAAs treatment. In fact, the investigators note other factors could explain the higher incidence of cancer. The study analysis showed that the shorter duration of follow-up and older age of participants rather than the treatment regimen could be responsible for higher incidence of HCC. On meta-regression, DAA therapy was not significantly associated with HCC occurrence (relative risk [RR], 0.7; P = .6) or recurrence (RR, 1.4; P = .49) [21].

In a Scottish study, the risk for liver cancer after sustained virologic response was not significantly different between patients treated with IFN-free therapy and those treated with IFN-based therapy [21]. Of the 857 cirrhotic patients treated at one of 12 clinics in Scotland, 32% were treated with DAA regimens. During a median follow-up of 1.8 years, fewer patients in the interferon-free group than in the interferon group developed HCC (12 vs. 34). Even so, the risk was significantly higher in the IFN-free group (incidence rate ratio [IRR], 2.18; P = .03) [21].

5.3.3. DAAs cut risk of liver cancer

Eradicating hepatitis C with DAA therapy reduces the risk of HCC by 71%, according to results of a large observational study [22]. The findings are based on 62,051 patients who underwent 83,695 antiviral treatment regimens in the VA Puget Sound Health Care System. The data included 35,873 IFN-only regimens, 26,178 DAA regimens with or without IFN, and 21,644 DAA-only regimens. The researchers identified 3271 new cases of liver cancer diagnosed at least 180 days after the start of antiviral treatment during an average follow-up of 6.1 years. The incidence of liver cancer was highest in patients with cirrhosis who failed treatment (3.25 per 100 patient-years)—followed by patients with cirrhosis and sustained virologic response, or SVR, (1.97), no cirrhosis and treatment failure (0.87), and no cirrhosis and SVR (0.24). In multivariable models adjusted for potentially confounding factors, SVR was associated with a significantly reduced risk of liver cancer, regardless of whether the antiviral treatment was DAA-only (adjusted hazard ratio (aHR), 0.29), DAA with IFN (aHR, 0.48), or IFN-only (aHR, 0.32). In both cirrhotic and non-cirrhotic patients, the risk of liver cancer was reduced [22].

5.4. Viral resistance

The huge genetic diversity due to poor fidelity of its replication enzyme (i.e., RdRp) and rapid replication rate configures HCV genome into 7 distinct GTs, more than 84 subtypes, and even exists as a quasispecies in a single-infected patient [2]. The viral genome differs by >30% at GT level, >15% at subtypes level, and <15% within a specific GT (i.e., quasispecies) in an infected individual. This genome variation by nucleotide substitutions/mutations is considered a major reason for the origination of pre-existing or treatment-emergent RASs in DAA-treated patients [2, 23]. Baseline polymorphism and pre-existing or treatment-emergent RASs are the most considerable points to the physicians while deciding to initiate oral IFN-free DAAs for hepatitis C treatment in treatment-naive (TN) or treatment-experienced (TE) or treatment-failure patients [23]. It is a well-established fact that viral mutations make the virus less susceptible to treatment; and in the case of HCV, it has been proven that monotherapy will result in selection of mutations which enhance replication in the presence of a drug. HCV resistance occurs when nucleotide substitutions randomly appear throughout the genome with every replication cycle. Some nucleotide substitutions by chance intervene to bind specific DAAs to their specific protein target [23].

Viral variants with RASs in the presence of DAAs possess a fitness advantage, but in the absence of DAAs, most will be outcompeted by a wild-type virus [23, 24]. The viral fitness of specific RASs potentially determines whether RASs persist after unsuccessful DAA therapy and whether they exist at baseline in TN patients. Interestingly, RASs to different DAA classes express markedly different viral fitness. The knowledge of RAS may influence clinical management of HCV in terms of alter duration of therapy, to add RBV in specific difficult-to-treat subpatient populations and severity of disease (cirrhotic vs. non-cirrhotic) and to choose particular DAA regimen for retreatment. Interestingly, some RASs affect the treatment response to all members of a specific DAA class, whereas others have variable impact on different DAAs of the same class. Meanwhile, the prevalence and effects of RASs vary in different populations (i.e., within different HCV GT/subtypes and quasispecies, individual RASs may differ in emergence and differently impact SVR rates) and may be more relevant in TE patients and those with cirrhosis [23, 24].

Unfortunately, still there are no clear guidelines for resistance testing. Should it be a universal testing of all patients' pretreatment or selective? As we have seen that SVR rates approach almost 100% for most HCV-treated patients while administered to most DDA regimens [24], it is difficult to do for everyone. However, this approach is only applicable to test those patients where knowledge of the findings may influence clinical management although which patients are those is a big question [23]. AASLD in 2017 recommends NS5A RASs testing for LDV/SOF and EBR/GZR combination prior to initiate therapy among GT 1 patients by virus subtype, prior TE, and cirrhosis status [23]. For GT 3, RASs detection is recommended for SOF/DCV or SOF/VEL combination and both for TE and cirrhotic patients, and if Y93H is present, weight-based RBV is added to active regimens. In contrast, current EASL recommendations demonstrate that access and affordability to reliable HCV resistance testing are limited, and there is limited consensus on the techniques used, data interpretation, and reporting of these detections. Surprisingly, EASL does not enforce HCV resistance testing prior to treatment and applies only to TE patients who were previously treated with PEG-IFN/RBV, PEG-IFN/RBV/SOF, SOF/RBV, etc. [24].

6. Conclusions

The present is pretty great, and the future is extremely positive after the advent and approval of IFN-free DAAs to cure hepatitis C. We will continue to push boundaries and now are at a point that we should be able to eradicate hepatitis C with these drugs. The journey started from an NS5B inhibitor (sofosbuvir) to develop pan-genotypic regimens that offer new perspectives in HCV screening and medicine. One size does not fit all; however, in the case of HCV, we are at the edge of brick where a single pill could be effective for all HCV genotype-infected populations in the near future. Thus new therapies afford public health policy makers great opportunities but, equally, pose dilemmas too where their cost has sparked much controversy and debate over who should get them, and HCC recurrence and HBV reactivation are key obstacles preventing to achieve global goal of HCV elimination. With curative treatment options available for patients with HCC and HBV, linkage to care and adherence to screening/surveillance guidelines should be clearly warranted for early diagnosis of HCC and HBV. Now, our aim should be to stimulate discussion as to how we can capitalize on the opportunities that new therapies will bring in terms of their expected population-level impact and engineer our treatment strategies accordingly. Overall, the future of HCV therapeutics seems bright and becomes brighter every day as treatment combinations continue to be designed, developed, and approved.

Author details

Imran Shahid[1,2]*

*Address all correspondence to: iyshahid@uqu.edu.sa

1 Department of Pharmacology and Toxicology, College of Pharmacy, Umm-Al-Qura University, Makkah, Saudi Arabia

2 Applied and Functional Genomics Laboratory, Center of Excellence in Molecular Biology (CEMB), University of the Punjab, Lahore, Pakistan

References

[1] Shahid I, ALMalki WH, Hafeez MH, Hassan S. Hepatitis C virus infection treatment: An era of game changer direct acting antivirals and novel treatment strategies. Critical Reviews in Microbiology. 2016;**42**(4):535-547. DOI: 10.3109/1040841X.2014.970123. Epub 2014 Nov 6

[2] Shahid I, AlMalki WH, Hassan S, Hafeez MH. Real-world challenges for hepatitis C virus medications: A critical overview. Critical Reviews in Microbiology. 2018;**44**(2):143-160. DOI: 10.1080/1040841X.2017.1329277. Epub 2017 May 25

[3] Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. Nature. 2005;**436**:967-972. DOI: 10.1038/nature04082

[4] Alter HJ, Seeff LB. Recovery, persistence and sequelae in hepatitis C virus infection: A perspective on the long-term outcome. Seminars in Liver Disease. 2000;**20**(1):17-35

[5] Fishman JA, Rubin RH, Koziel MJ, BJ P. Hepatitis C virus and organ transplantation. Transplantation. 1996;**62**(2):147-154

[6] Pham TNQ, Coffin CS, Michalak TI. Occult hepatitis C virus infection: What does it mean? Liver International. 2010;**30**:502-511. DOI: 10.1111/j.1478-3231.2009.02193.x

[7] Zekri AR, Hafez MM, Bahnassy AA, Hassan ZK, Mansour T, Kamal MM, et al. Genetic profile of Egyptian hepatocellular-carcinoma associated with hepatitis C virus Genotype 4 by 15 K cDNA microarray: Preliminary study. BMC Research Notes. 2008;**29**(1):106. DOI: 10.1186/1756-0500-1-106

[8] Ura S et al. Differential microRNA expression between hepatitis B and hepatitis C leading diseases progression to hepatocellular carcinoma. Hepatology. 2009;**49**(4):1098-1112. DOI: 10.1002/hep.22749

[9] Cannon CP. Mixed dyslipidemia, metabolic syndrome, diabetes mellitus, and cardiovascular disease: Clinical implications. The American Journal of Cardiology. 2008;**102**:5-9. DOI: 10.1016/j.amjcard.2008.09.067

[10] Wong RJ, Gish RG. Metabolic manifestations and complications associated with chronic hepatitis C virus infection. Journal of Gastroenterology and Hepatology. 2016;**12**:293-299

[11] Maticic M, Poljak M, Seme K, Brinovec V, Meglic-Volkar J, Zakotnik B, et al. Detection of hepatitis C virus RNA from gingival crevicular fluid and its relation to virus presence in saliva. Journal of Periodontology. 2001;**72**(1):11-16. DOI: 10.1902/jop.2001.72.1.11

[12] Jovanovic-Cupic S, Kokanov N, Petrovic N, Krajnovic M, Kozik B, Kojic M, et al. The influence of baseline viral and host factors on therapy response in patients with chronic hepatitis C genotype 1b from Serbia. In: First Congress of Molecular Biologist Congress of Molecular Biologists of Serbia with International Participation; 20-22 September 2017; Belgrade, Serbia. p. 135

[13] Imran Shahid, Waleed H. AlMalki, Mohammed W. AlRabia, Muhammad H. Hafeez and Muhammad Ahmed. Hepatitis C virus infection treatment: Recent advances and new paradigms in the treatment strategies, Advances in Treatment of Hepatitis C and B, Prof. Naglaa Allam editor. Rijeka, Croatia: InTech; 2017. DOI: 10.5772/65873. Available from: https://www.intechopen.com/books/advances-in-treatment-of-hepatitis-c-and b/hepatitis-cvirus-infection-treatment-recent-advances-and-new-paradigms-in-the treatment-strategies

[14] FDA Clears Pan-Genotypic *Vosevi* for Chronic Hepatitis C. Available from: https://www.medscape.com/viewarticle/883095 [Accessed: 15-08-2018]

[15] FDA OKs 8-Week *Mavyret* for Hepatitis C. Available from: https://www.medscape.com/viewarticle/883778 [Accessed: 25-07-2018]

[16] Glecaprevir/Pibrentasvir Treats Hepatitis C in HIV-Coinfected Individuals. Available from: https://www.medscape.com/viewarticle/894696 [Accessed: 23-08-2018]

[17] Shorter Anti-HCV Regimen Effective in Patients With or Without Cirrhosis. Available from: https://www.medscape.com/viewarticle/884478 [Accessed: 09-08-2018]

[18] HCV Drugs May Reactivate HBV, FDA Warns. Available from: https://www.medscape.com/viewarticle/869784 [Accessed: 15-07-2018]

[19] EMA to Review New Hep C Drugs for Possible Hep B Reactivation. Available from: https://www.medscape.com/viewarticle/860609 [Accessed: 17-07-2018]

[20] Direct-Acting Antivirals for Hep C Might Worsen Liver Cancer. Available from: https://www.medscape.com/viewarticle/871831 [Accessed: 20-07-2018]

[21] Navigating the Hep C Treatment and Cancer Risk Minefield. Available from: https://www.medscape.com/viewarticle/881041 [Accessed: 06-08-2018]

[22] Direct-Acting Antivirals Cut Risk of Liver Cancer. Available from: https://www.medscape.com/viewarticle/887434 [Accessed: 28-07-2018]

[23] Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology. 2016;**151**:70-86. DOI: 10.1053/j.gastro.2016.04.003

[24] Shahid I, Ibrahim MM, Nawaz MU, Imam MT, AlMalki WH. Resistance-associated substitutions/variants correlate to therapeutic outcomes of novel direct-acting antivirals in different HCV genotype treated individuals. In: Abdurakhmonov I, editor. Genotyping. Rijeka, Croatia: IntechOpen; 2018. DOI: 10.5772/intechopen.76395. Available from: https://www.intechopen.com/books/genotyping/resistance-associated-substitutions-variants-correlate-to-therapeutic-outcomes-of-novel-direct-actin

IntechOpen

IntechOpen