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Reinventing HCV Treatment: Past and Future Perspectives

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Abstract

This review paper summarizes the epidemiology of hepatitis C virus (HCV) and chronic HCV infection, including HCV virology and treatment regimens. Specifically, we focus on the evolution of past, current, and future HCV treatment options, the reasons for treatment failure, and the impact of resistance-associated variants on treatment success.

Keywords

hepatitis C, direct-acting antivirals, genotype, sustained virologic response, resistance-associated variants

Epidemiology, Presentation, and Natural History of HCV Disease

The hepatitis C virus (HCV) is a positive-strand RNA virus identified in 1989 and belonging to the *Flaviviridae* family, which includes other human pathogens such as dengue, West Nile, and yellow fever viruses.[1] At least 7 HCV genotypes (GT) have been identified, each with a distinct geographic distribution; most HCV genotypes are divided into multiple subtypes (eg, HCV GT 1a and 1b).[2] The most common HCV GT in the United States is GT 1 (70% to 75%), followed by GT 2 and 3 (20% to 25%). HCV GT 4, 5, and 6 represent <1% to 6% of HCV genotypes in the United States.[3–5] HCV GT 7 has been recently reported in patients from the Democratic Republic of Congo.[6]

HCV is predominantly a bloodborne pathogen, and no vaccine is currently available to prevent HCV acquisition. The development of an effective vaccine for HCV has been met with multiple challenges, the paramount challenge being the extreme diversity of the HCV virus, with >30% divergence between each of the 7 major HCV genotypes at the amino acid level.[7] Additionally, despite recent gains in knowledge about the immunologic response to HCV, the key elements for a successful immune response remain unknown.[8] Approximately 20% of persons exposed to HCV will clear the virus; however, the majority will develop chronic HCV infection. Over years to decades, patients may develop complications resulting from chronic HCV infection, such as cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC), which may lead to liver transplantation or death.[9] Persons with associated HIV infection or who use alcohol may have an accelerated disease progression.[10]

Chronic HCV infection is both a global and a domestic public health issue, with approximately 170 million people infected worldwide and approximately 3.5 million people infected in the United States, although these prevalence reports may be underestimations.[11–13] In the United States, chronic HCV infection is currently the most common reason for liver transplantation, and an estimated 19,000 deaths occur each year related to the disease. This rate of deaths is more than the total combined deaths from 60 other infectious diseases, including HIV.[12,14,15] Many people are unaware of their infection, and the CDC and US Preventive Services Task Force now recommend screening all persons born between 1945 and 1965 to identify those with HCV infection. Although this birth cohort compromises approximately 25% of the US population, the 1945-1965 birth cohort accounts for approximately 75% of all HCV infections in the United States.[16]

With the aging of the infected population and without effective HCV treatment, it is estimated that by 2019-2020 there could be approximately 145,000 annual cases of decompensated cirrhosis and 14,000 cases of HCC.[17]

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HCV Virology

The main challenges to development of effective therapy have been the need for appropriate models and the deciphering of the complex HCV life cycle in order to study the disease. The chimpanzee has been the only true HCV animal model and was critical for studies of pathogenesis and HCV immunity.[18] Subsequently, human-liver chimeric and genetically modified HCV-permissive mouse models were developed. The lack of a cell culture system was a major obstacle to the understanding of the HCV life cycle. However, development of selectable replicon systems led to the understanding of HCV replication while retrovirus-based pseudotyped particles led to further knowledge about viral entry. In 2005, complete viral replication systems allowed for the investigation of the whole HCV viral life cycle.[19] These important scientific advances, particularly the development of the HCV replicon system, allowed exploration of ways to interrupt the HCV life cycle and led to more rapid evaluation of potential drug candidates.

Several main steps occur in the HCV life cycle and include binding and entry, translation, maturation, replication, assembly, and release. Each of these steps offers opportunities for development of drugs to interrupt the life cycle of the virus. In contrast to interferon α (IFN), which induces the body's innate antiviral immune response, direct-acting antivirals (DAAs) are designed to directly inhibit viral proteins involved in the HCV life cycle. Three important HCV DAA classes are highlighted: (1) NS3/4A protease inhibitors, which inhibit HCV polyprotein processing, (2) NS5B polymerase inhibitors, which inhibit HCV RNA replication, and (3) NS5A inhibitors, which inhibit viral replication and assembly, although the precise mechanism of action is unknown.[20] HCV DAA monotherapy in phase 1 trials often resulted in emergence of drug-resistant virus in study volunteers, particularly when drugs with a low resistance barrier were administered.[21–23] Thus as the development of effective HCV treatment options moved away from IFN-containing regimens, combination therapies from different HCV DAA classes with nonoverlapping resistance mechanisms became a focus of drug development.

Goals of Therapy: Virologic Cure

Goals of successful HCV therapy include both HCV viral clearance and improved clinical outcomes. The efficacy endpoint used in HCV clinical trials and in clinical practice is called sustained virologic response (SVR), defined as a lack of detection of HCV RNA in the blood at a certain time period, measured in weeks, after treatment is completed. Achieving SVR correlates with improved clinical outcomes such as decreased HCC, hepatic events, fibrosis, and all-cause mortality, and therefore it is considered a virologic cure of chronic HCV infection.[24–28]

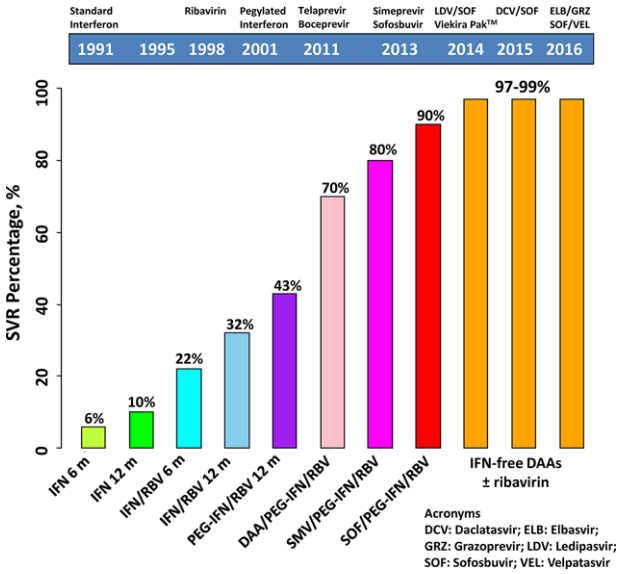

Figure 1. SVR rates over time by treatment regimen for HCV genotype 1. SVR, sustained virologic response; HCV, hepatitis C virus; m, month; IFN, interferon; RBV, ribavirin; PEG-IFN, pegylated interferon; DAA, direct-acting antiviral; SMV, simeprevir. Data from references 30,31,33–37,39–50.

The FDA examined the correlation between SVR12 (that is, achieving SVR 12 weeks after completing HCV treatment) and SVR24 in more than 13,000 subjects pooled from multiple clinical trials of IFN-based regimens and found a high rate of concordance between SVR12 and SVR24.[29] Sensitivity and specificity for SVR12 were 99% and 98%, respectively; therefore, SVR12 is considered a suitable primary endpoint for HCV registrational trials.

Brief History of HCV Treatment

HCV Genotype 1

Treatment of HCV has undergone revolutionary change within the past 25 years. As stated previously, HCV GT 1 is the most common genotype in the United States and, in the era of IFN-based treatment regimens, was historically the most difficult to treat successfully. Figure 1 depicts the evolution of treatment options and dramatic improvement in attainment of SVR for patients with HCV GT 1 infection. With the original approval of standard IFN used 3 times per week for 6 months, SVR rates were approximately 6%. In 1998, the FDA approved the first combination of IFN and ribavirin (RBV). RBV is a synthetic nucleoside analogue with broad antiviral activity that was originally developed for possible treatment of HIV-1 infection. However, RBV was not effective against HIV-1, and due to RBV's activity against some flaviviruses, RBV

was studied as a single agent for treatment of HCV. Clinical findings of reduction in ALT led to use of RBV in combination with IFN, which was found to have synergy and improve SVR rates. Adding RBV, and prolonging the duration of therapy for 48 weeks, caused SVR rates for HCV GT 1 to improve to approximately 32%; SVR rates for HCV GT 2 to 6 were approximately 59%.[30,31] However, limited data were available for treatment of HCV GT 4, 5, and 6 with IFN/RBV, which suggested a need to treat these patients like HCV GT 1 patients.[32]

In 2001-2002, FDA approvals of 2 pegylated interferon (pegIFN) products further improved HCV GT 1 SVR rates to approximately 43% in combination with RBV.[33,34] Pegylation is a process that attaches polyethylene glycol, an inert compound, to the IFN molecule and is used to increase IFN concentrations and decrease clearance, allowing for more sustained and higher concentrations of IFN over a prolonged dosing period to increase the likelihood of achieving SVR. As mentioned above, development of the HCV replicon system in 2005 allowed for advancement of many new drugs into the development pipeline. However, the first 2 HCV DAAs were not approved until 2011.

In 2011, telaprevir (Incivek) and boceprevir (Victrelis), both NS3/4A protease inhibitors, were approved for use in combination with pegIFN and RBV for treatment of HCV GT 1. Although SVR rates improved to approximately 70% for patients with HCV GT 1, these triple-drug regimens had substantial tolerability issues with additional side effects, including severe anemia, serious skin reactions or rash, and dysgeusia, which added to the underlying tolerability issues associated with pegIFN and RBV (fatigue, rash, anemia, neutropenia, and psychiatric issues, including suicidal or homicidal ideation).[35,36] In 2013, simeprevir (Olysio) in combination with pegIFN + RBV for 24 weeks was approved for HCV GT 1, and sofosbuvir (Sovaldi) in combination with pegIFN + RBV for 12 weeks was approved for treatment of HCV GT 1 and GT 4. The SVR rate for treatment-naive HCV GT 1 with simeprevir + pegIFN + RBV was approximately 80%, and the shorter duration sofosbuvir + pegIFN + RBV approximately 90%.[37,38]

In 2014, a new era of IFN-free HCV DAA therapies was ushered in with the approvals of the combination regimens of ledipasvir/sofosbuvir (Harvoni) and the "3D" regimen ombitasvir/paritaprevir/ritonavir tablets in combination with dasabuvir (Viekira Pak). SVR rates improved to 90% or above for HCV GT 1, and the treatment indications for these DAAs were subsequently expanded to include certain other HCV GTs. Additional HCV DAA-based regimens including daclatasvir (Daklinza) + sofosbuvir and elbasvir/grazoprevir (Zepatier) were approved in 2015 and 2016, respectively, providing additional treatment options for patients with HCV GT 1 infection.[39–42] In June 2016, sofosbuvir/velpatasvir (Epclusa) was approved; this regimen is the first indicated to treat all 6 major HCV GTs (GT 1-6). Following a 12-week regimen of sofosbuvir/velpatasvir, SVR rates of 95% to 100% were seen across the various GTs evaluated in phase 3 trials.[43]

HCV Genotype 3

In the era of HCV DAA-based regimens, HCV GT 3 has generally resulted in lower overall SVR rates and higher relapse rates compared to other genotypes. Historically, treatment with standard IFN in the early 1990s provided an SVR rate of 30% for patients with HCV GT 3. The addition of RBV to the regimen in 1998 improved SVR rates to 65%.[30,31,51] PegIFN and RBV combination therapy in 2001 provided an incremental increase to HCV GT 3 SVR rates to approximately 70% whether treatment was given for 6 months or 1 year.[33,34,46,47] The 2013 approval of the first IFN-free, HCV DAA-containing regimen of SOF + RBV provided an improvement in HCV GT 3 SVR rates to 84%.[37] Further incremental increase in HCV GT 3 SVR rates to 89% occurred with the 2015 approval of daclatasvir + sofosbuvir for 12 weeks, the first pegIFN- and RBV-free HCV DAA regimen indicated for HCV GT 3.[42] However, with the approval of sofosbuvir/velpatasvir, SVR rates for HCV GT 3 improved to 95% (see Figure 2).[43]

Currently Available DAA HCV Treatment

Multiple DAA-based regimens are currently approved that provide 1 or more IFN-free treatment options for HCV GTs 1 through 6. The choice of a DAA treatment regimen, duration of therapy, and use of RBV depends on multiple viral and host factors, including but not limited to HCV genotype, prior treatment experience, presence of cirrhosis (compensated or decompensated), history of liver transplantation, presence of renal disease, presence of HIV coinfection, presence of baseline resistance-associated variants (RAVs), and the potential for significant drug-drug interactions. Treatment guidelines for chronic HCV infection published jointly from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) are available and updated regularly online at www.hcvguidelines.org for detailed recommendations for testing, managing, and treating hepatitis C. Currently available HCV DAA drugs are listed in Table 1.

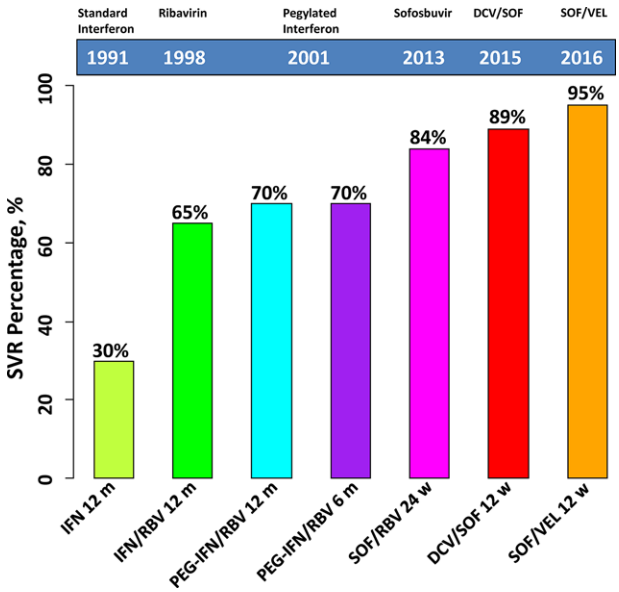

Figure 2. SVR rates over time by treatment regimen for HCV genotype 3, SVR, sustained virologic response; HCV, hepatitis C virus; m, month; IFN, interferon; RBV, ribavirin; PEG-IFN, pegylated interferon; SOF, sofosbuvir; DCV, daclatasvir; VEL, velpatasvir. Data from references 30,31,33,34,37,42, 43,46,47,49,51.

Treatment of Subpopulations

Some subpopulations previously unable to receive an IFN-based regimen are now able to be treated with an HCV DAA regimen, as use of interferon was contraindicated in patients with decompensated cirrhosis. However, now ledipasvir/sofosbuvir + RBV for 12 weeks and daclatasvir + sofosbuvir + RBV for 12 weeks are approved for treatment of patients with decompensated cirrhosis and HCV GT 1 or HCV GT 1 or 3, respectively. Sofosbuvir/velpatasvir + RBV for 12 weeks is also approved for treatment of patients with decompensated cirrhosis and HCV GT 1, 2, 3, 4, 5, or 6 infection.

Similarly, patients with significant renal disease had limited or no treatment options available prior to the approval of IFN-free HCV DAA regimens. The fixed-dose combination of elbasvir/grazoprevir requires no dosage adjustment in patients with any degree of renal impairment, including hemodialysis; however, RBV is still required for some populations, and HCV GT 2 or GT 3 patients with ESRD or GFR <30 still have no FDA-approved treatment options.

Historically, patients with HIV-1/HCV coinfection had lower response rates and were more likely to have significant comorbidities and adverse events associated with treatment with IFN-based therapy.[52,53] Data from multiple trials of HCV DAA-based regimens demonstrate that patients with HIV-1/HCV coinfection attain similar SVR rates to those with HCV monoinfection. Now, one of the most important factors in initiating an appropriate treatment regimen in patients with HIV-1/HCV coinfection is a consideration of the potential for complex drug-drug interactions with antiretrovirals. Further discussion of the various challenges of treating some subpopulations is highlighted in the following section.

Table 1. Currently Available HCV DAAs by Drug Class

Drug Class	Generic Name	Trade Name	HCV Genotype With Approved Indication
NS3A/4A protease inhibitors	Simeprevir	Olysio®[45]	1, 4
	Paritaprevir (fixed-dose combination product with ritonavir, ombitasvir, and copackaged with dasabuvir)	Viekira Pak®[40]	1
	Paritaprevir (fixed-dose combination product with ombitasvir, ritonavir)	Technivie®[44]	4
	Grazoprevir (fixed-dose combination product with elbasvir)	Zepatier™[41]	1, 4
NS5B polymerase inhibitors—nucleotide	Sofosbuvir	Sovaldi®[37]	1, 2, 3, 4
NS5B polymerase inhibitors—nonnucleoside	Dasabuvir (copackaged with fixed-dose combination product ombitasvir, paritaprevir, ritonavir)	Viekira Pak®[40]	1
NS5A inhibitors	Ledipasvir (fixed-dose combination product with sofosbuvir)	Harvoni®[39]	1, 4, 5, 6
	Ombitasvir (fixed-dose combination product with paritaprevir, ritonavir, and copackaged with dasabuvir)	Viekira Pak®[40]	1
	Ombitasvir (fixed-dose combination product with paritaprevir, ritonavir)	Technivie®[29]	4
	Daclatasvir	Daklinza™[42]	1, 3
	Elbasvir (fixed dose combination product with grazoprevir)	Zepatier™[41]	1, 4
	Velpatasvir (fixed-dose combination product with sofosbuvir)	Epclusa®[43]	1, 2, 3, 4, 5, 6

HCV, hepatitis C virus; DAA, direct-acting antiviral.

Reasons for Treatment Failure

Historically, following treatment with pegIFN and RBV, lower SVR rates were observed in HCV GT 1–infected patients and in patients with HCV RNA greater than 600,000 IU/mL. Other baseline characteristics seen in patients with lower SVR rates included male sex, advanced liver fibrosis or cirrhosis, HIV and HBV coinfection, insulin resistance, poor treatment adherence, IL28B status, and African ancestry.[32,54] More recently, in phase 3 trials, treatment with pegIFN-free HCV DAA-based regimens resulted in SVR12 rates greater than 93% for HCV GT 1 subjects with compensated liver disease. SVR12 rates exceed 93% for HCV GTs 4, 5, and 6 with similar rates of relapse compared to HCV GT 1; however, the numbers of subjects with HCV GTs 5 and 6 are limited in phase 3 trials. For HCV GT 2, SVR rates range from 82% to 99% in phase 3 trials. SVR rates are lower in HCV GT 3 subjects compared to HCV GT 1 subjects, particularly those who are treatment-experienced and cirrhotic.

The vast majority of treatment failures for HCV DAA-based regimens are due to posttreatment virologic relapse. The significance of the factors associated with lower SVR rates with current HCV DAA regimens may differ from those factors noted for IFN-based regimens. Lower SVR rates observed for IFN-free, HCV DAA-based regimens may be due to host factors such as cirrhosis status or prior treatment history; or they may be due to viral factors such as HCV GT and subtype, presence of baseline resistance-associated variants (RAVs); or due to suboptimal adherence or duration of treatment.[55,56] Additionally, genetic barriers to resistance differ among HCV DAA drug classes and can also impact SVR rates.[23] Often a combination of baseline factors impact SVR rates, and 1 clear dominant baseline factor is not possible to discern. The following section focuses specifically on the impact of baseline RAVs, HCV GT and subtype, cirrhosis status, and prior treatment history on SVR rates with DAA regimens.

Impact of Resistance-Associated Variants

HCV replicates rapidly with a daily production of 10^{12} virions and has a high error rate, which results in RAVs naturally produced during the replication cycle.[57,58] In some individuals these RAVs predominate as natural polymorphisms in the viral population (and thus are more specifically referred to as "resistance-associated polymorphisms") and may impact DAA-based treatment efficacy. The hallmark example is the NS3 Q80K polymorphism effect on simeprevir SVR rates. The Q80K baseline polymorphism is found in 5% to 48% of HCV GT 1a subjects.[59] Following treatment with a simeprevir + pegIFN + RBV regimen, SVR12 rates were substantially lower in HCV GT 1a treatment-naive subjects with the NS3 Q80K polymorphism at baseline (58%) compared to HCV GT 1a treatment-naive subjects without the Q80K polymorphism (84%). Similar findings were seen for treatment-experienced HCV GT 1a subjects. As a result, screening patients with HCV GT 1a infection for the presence of the Q80K baseline polymorphism is strongly recommended in labeling prior to the initiation of simeprevir + pegIFN + RBV. Alternative HCV therapy should also be considered for patients with HCV GT 1a and the Q80K polymorphism.[45]

The role of baseline NS5A polymorphisms has also gained interest recently. The prevalence of baseline NS5A polymorphisms can vary by trial depending on which polymorphisms are included and the methodology used to detect NS5A polymorphisms. Recent phase 3 clinical trials show the prevalence of baseline NS5A RAVs in HCV GT 1 subjects ranged from 11% to 32% and were approximately 20% in HCV GT 3–infected subjects.[41–43] NS5A RAVs may reduce SVR rates for certain regimens. With the recent approval of elbasvir/grazoprevir, testing for the presence of baseline RAVs at amino acid positions 28, 30, 31, or 93 is recommended for patients with HCV GT 1a. The testing recommendation was based on a phase 3 trial in which treatment with elbasvir/grazoprevir for 12 weeks showed that HCV GT 1a–infected subjects with baseline NS5A RAVs had lower SVR rates (70%) than HCV GT 1a–infected subjects without NS5A RAVs (98%). In HCV GT 1a subjects with baseline NS5A RAVs, the recommendation is to add RBV to elbasvir/grazoprevir and extend the treatment duration to 16 weeks.[41] In one phase 3 trial that evaluated the longer 16-week duration of elbasvir/grazoprevir with and without RBV, no HCV GT 1a subjects with baseline NS5A RAVs experienced virologic relapse. The number of patients with baseline NS5A RAVs was limited; however, the data suggest that addition of RBV and extended duration (16 weeks) may help to improve treatment responses in subjects with baseline polymorphisms.[60]

For the paritaprevir/ritonavir/ombitasvir + dasabuvir (3D) regimen, the SVR12 rates reported from phase 3 trials showed no difference in SVR rates in HCV GT 1a–treatment-experienced subjects treated with the label-recommended regimens of 3D with RBV for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis), regardless of the presence or absence of baseline NS5A RAVs (95% to 98%).[61,62] Similarly, HCV GT 1b treatment-experienced subjects treated with 3D for 12 weeks had similar SVR rates regardless of the presence or absence of baseline NS5A RAVs.[63]

A study by Sarrazin et al evaluated the impact of baseline NS5A RAVs on SVR rates in HCV GT1 subjects receiving ledipasvir/sofosbuvir, with or without RBV, in the phase 2 and 3 trials. In general, baseline NS5A RAVs had minimal impact on SVR rates based

on next-generation nucleotide sequencing analyses (1% variant detection cutoff). For HCV GT 1 subjects receiving ledipasvir/sofosbuvir, SVR rates were 98% (1741/1770) for those without baseline NS5A RAVs and 94% (316/338) for those with baseline NS5A RAVs. Interestingly, SVR rates were reduced in certain HCV GT 1 populations with baseline NS5A RAVs conferring >100-fold resistance to ledipasvir. In treatment-naive subjects receiving a shorter 8-week duration of ledipasvir/sofosbuvir, SVR rates were 96% for those with no baseline NS5A RAVs, 100% for those with baseline NS5A RAVs conferring <100-fold resistance to ledipasvir, and 83%, for those with >100-fold resistance to ledipasvir. In contrast, in treatment-naive subjects receiving ledipasvir/sofosbuvir for 12 or 24 weeks, SVR rates ranged from 96% to 100% regardless of the presence or absence of baseline NS5A RAVs, and regardless of the degree of baseline resistance to ledipasvir (<100-fold or >100-fold). Additionally, SVR rates were reduced in treatment-experienced subjects who received ledipasvir/sofosbuvir for 12 weeks and had baseline NS5A RAVs with >100-fold resistance to ledipasvir (65%) compared to treatment-experienced subjects without baseline NS5A RAVs or baseline NS5A RAVs with <100-fold resistance to ledipasvir (97% to 100%). SVR rates were 100% in treatment-experienced subjects who received ledipasvir/sofosbuvir for 24 weeks whether baseline NS5A RAVs were present or not and irrespective of any degree of resistance to ledipasvir at baseline; however, these results are based on a limited number of subjects (n = 13). These data suggest that a shorter duration of ledipasvir/sofosbuvir (8 weeks) in HCV GT 1 treatment-naive subjects and 12 weeks in HCV GT 1 treatment-experienced subjects may not be sufficient to overcome baseline NS5A RAVs conferring >100-fold resistance to ledipasvir.[64]

Trials in non-HCV GT 1 populations also show the effect of baseline RAVs on SVR rates. In HCV GT 3 subjects treated with daclatasvir+sofosbuvir for 12 weeks, SVR rates were affected by the presence of the baseline NS5A RAV Y93H and cirrhosis. Among subjects with HCV GT 3 infection, the overall SVR rates were reduced from 92% (149/162) in subjects without the Y93H RAV to 54% (7/13) in subjects with the Y93H RAV. Furthermore, SVR12 rates were reduced by approximately 30% in subjects with cirrhosis compared to those without cirrhosis (96% vs 63%) and were further reduced to 25% (1/4) in subjects with the Y93H RAV and cirrhosis compared to 71% (24/34) in subjects without the Y93H RAV and cirrhosis[42]; however, these results are based on limited numbers of subjects within the smaller subgroup of HCV GT 3 patients within the overall HCV population in the United States.

Overall, the virologic relapse rate in HCV GT 3 subjects treated with sofosbuvir/velpatasvir was 4% (11/275). The relapse rate was higher in HCV GT 3 subjects with baseline NS5A RAVs (7%; 4/56) compared to HCV GT 3 subjects without baseline NS5A RAVs (3%; 7/218). Furthermore, relapse rates were also higher in HCV GT 3 subjects with cirrhosis and baseline NS5A RAVs (33%; 3/9) compared to subjects with cirrhosis and no baseline NS5A RAVs (6%; 4/71). All of these examples underscore the complexity and various combination baseline factors (viral and host) that affect SVR rates.

In product labeling, baseline resistance testing is currently not routinely considered or recommended for initiating first-time HCV treatment, with the exception of simeprevir and elbasvir/grazoprevir, and for HCV GT 1a patients with cirrhosis prior to initiation of daclatasvir+sofosbuvir with or without RBV. Resistance testing is not considered or recommended either due to the overall high SVR rates (>90%), or because such strategies are helpful only if the test is commercially available and if the test result guides a change in management strategy for subjects with RAVs, such as treatment with a different HCV DAA regimen, prolonging the course of treatment, or adding another agent such as RBV. For example, because an ideal, IFN-free and RBV-free alternative treatment regimen for HCV GT 3 patients with the presence of the NS5A RAV Y93H was not approved, and the prevalence of the baseline RAV was approximately 10% of the those with HCV GT3 infection, representing a small subset of the overall US HCV population, a screening recommendation for daclatasvir was not considered critical at the time of approval.

In the near future, resistance testing may become more important to guide the choice of a subsequent treatment regimen after treatment failure with an HCV DAA-based regimen.[59] However, at this time, retreatment data in patients with a prior failure of a HCV DAA regimen, particularly for a NS5A-based regimen, are limited.

Impact of HCV Genotype Subtype

HCV GT subtype, specifically HCV GT 1a and HCV GT 1b, has not played a substantial role in overall SVR rates for the IFN-free HCV DAA regimens; however, treatment differences up to 9% are observed for certain regimens in subjects with HCV GT 1a vs HCV GT 1b. No appreciable differences in SVR rates are noted between patients with HCV GT 1a vs 1b with daclatasvir + sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir + dasabuvir (+/– RBV) regimens. Numerically lower SVR rates are seen in HCV GT 1a (90% to 92%) compared to HCV GT 1b (96% to 100%) patients treated with

elbasvir/grazoprevir; however, the numerical difference in SVR rates may have been due to the inclusion of HCV GT 1a subjects with baseline RAVs who were not screened out in the clinical trial. HCV GT 1a vs 1b differences were more notably observed with DAA + pegIFN + RBV–based regimens. SVR rates for sofosbuvir + pegIFN + RBV are lower (83%) in subjects with HCV GT 1b compared to subjects with HCV GT 1a (92%). In contrast, with simeprevir + pegIFN + RBV, SVR rates were lower in HCV GT 1a compared to HCV GT 1b.

Impact of Cirrhosis Status and Prior Treatment History

Cirrhosis status remains an important baseline characteristic affecting SVR rates. SVR rates are, in general, numerically higher in HCV GT 1 subjects without cirrhosis compared to subjects with compensated cirrhosis. SVR rates are more notably higher in HCV GT 3 subjects without cirrhosis compared to subjects with compensated cirrhosis. Prior HCV treatment history in addition to cirrhosis status is another important factor in predicting SVR rates. Among subjects with compensated liver disease, HCV GT 3 treatment-experienced subjects with compensated cirrhosis have the lowest SVR rates. Trials in HCV GTs 4, 5, and 6 have enrolled limited numbers of subjects with prior treatment experience and with compensated cirrhosis; therefore, insufficient data are available to make definitive conclusions on the impact of cirrhosis status on SVR rates. Table 2 summarizes the SVR12 rates for the approved products by treatment history and cirrhosis status. SVR rates for sofosbuvir/velpatasvir for HCV GT3 by cirrhosis status are displayed in Table 2. SVR rates for HCV GT 1, 2, 4, 5, and 6 were 97% to 100% and were not affected by baseline compensated cirrhosis and therefore are not included in Table 2. Overall, in the sofosbuvir/velpatasvir phase 3 trials enrolling subjects with compensated liver disease, only 2 HCV GT 1 subjects had virologic relapse, and no HCV GT 2, 4, 5, or 6 subjects had virologic relapse.

Overall, the reasons for treatment failure to current IFN-free HCV DAA regimens are multifactorial. The interplay among HCV GT/subtype, cirrhosis status, prior HCV treatment history, and the presence of baseline RAVs further complicates the ability to predict treatment failure vs success on an individual level. Resistance testing, longer duration of treatment, and the addition of RBV or even IFN may be needed to minimize overall virologic failure rates for future retreatment regimens.

Table 2. SVR12 Rates by Regimen, Treatment History, and Compensated Cirrhosis Status

Regimen/Trial Name/Treatment History	Noncirrhotic	Compensated Cirrhosis
HCV Genotype 1		
Daclatasvir + sofosbuvir ×12 weeks		
ALLY-2 (TN/TE)	98% (103/105)	91% (20/22)
Ledipasvir/sofosbuvir		
ION-1 Trial (TN) ×12 weeks	99% (176/177)	94% (32/34)
ION-2 Trial (TE)		
×12 weeks	95% (83/87)	86% (19/22)
×24 weeks	99% (85/86)	100% (22/22)
ION-3 (TN)		
×8 weeks	94% (202/215)	NA
×12 weeks	96% (208/216)	NA
Simeprevir + sofosbuvir (TN/TE)		
COSMOS		
×12 weeks	95% (20/21)	86% (6/7)
×24 weeks	95% (20/21)	100% (10/10)
Paritaprevir/ritonavir/ombitasvir + dasabuvir (3D) regimen		
SAPPHIRE-I GT 1a (TN) ×12 weeks + RBV	96% (308/322)	NA
PEARL-IV GT 1a (TN) ×12 weeks + RBV	97% (97/100)	NA
SAPPHIRE-II GT 1a (TE) ×12 weeks + RBV	96% (166/173)	NA
PEARL II and III GT 1b (TN/TE) ×12 weeks	100% (300/300)	NA
TURQUOISE-II (TN/TE)		
GT 1a ×24 weeks + RBV	NA	95% (115/121)
GT 1a ×12 weeks + RBV	NA	89% (124/140)
TURQUOISE-III (TN/TE)		
GT 1b × 12 weeks	NA	100% (60/60)
Elbasvir/grazoprevir		
C-Edge (TN) × 12 weeks	94% (207/220)	97% (66/68)
C-Edge Coinfection (TN) × 12 weeks	94% (148/158)	100% (31/31)
C-Edge (TE)		
×12 weeks	94% (61/65)	94% (29/31)
×16 weeks + RBV	95% (61/64)	100% (35/35)
C-SURFER (TN/TE) × 12 weeks	95% (109/115)	86% (6/7)
HCV Genotype 2		
Sofosbuvir + RBV ×12 weeks		
FISSION (TN)	97% (59/61)	83% (10/12)
POSITRON (TN/TE)	92% (85/92)	94% (16/17)
FUSION (TE)	90% (26/29)	60% (6/10)
VALENCE		
TN	97% (29/30)	100% (2/2)
TE	91% (30/33)	88% (7/8)
HCV Genotype 3		
Daclatasvir + sofosbuvir ×12 weeks		
ALLY-3 (TN/TE)	96% (115/120)	63% (20/23)
Sofosbuvir + RBV ×24 weeks		
VALENCE		
TN	93% (86/92)	92% (12/13)
TE	85% (85/100)	60% (27/45)
Sofosbuvir/velpatasvir ×12 weeks		
ASTRAL-3		
TN	98% (160/163)	93% (40/43)
TE	94% (31/33)	89% (33/37)

RBV, ribavirin; TN, treatment naive; TE, treatment-experienced. Data from references 37–43.

The Future of HCV Treatment

Treatment of HCV has rapidly improved, moving from a poorly tolerated oral and injectable drug

combination to all oral, well-tolerated combination treatment options with virologic cures for over 90% of patients with chronic HCV. Treatment for HCV will continue to evolve over the next generation of therapies. Clinical goals of future treatment regimens include pangenotypic regimens with high barriers to resistance, simple dosing regimens, manageable drug-drug interaction profiles, shorter durations of therapy (<12 weeks), effective DAA retreatment options, and RBV-free regimens. The following discusses 2 examples of new therapeutic approaches; however, these are just a few examples of many ongoing development programs and novel strategies for treatment of HCV.

Another regimen with activity against the 6 major HCV GTs and with a high barrier to resistance, ABT-493/ABT-530, is in phase 3 development. In the phase 2 SURVEYOR-1 trial, ABT-493, a protease inhibitor, and ABT-530, an NS5A inhibitor, administered for 8 weeks to HCV GT 1 treatment-naive and treatment-experienced subjects without cirrhosis resulted in an SVR rate of 97% to 100%. SURVEYOR-2 evaluated HCV GT 2 and GT 3 treatment-naive and treatment-experienced subjects without cirrhosis who received 12 weeks of ABT-493/ABT-530. SVR rates were 96% to 100% in subjects with HCV GT 2 and 83% to 94% for HCV GT 3. The regimen was reported to be generally well tolerated, and further evaluation with phase 3 trials is ongoing.[65–67]

A regimen addressing retreatment of prior HCV DAA-experienced patients using a triple DAA fixed-dose combination regimen is also in development. The triple DAA regimen includes GS-9857 (voxilaprevir), an HCV NS3/4A protease inhibitor with activity against HCV GT1-6 and an improved resistance profile compared to older generation HCV protease inhibitors, along with the recently approved sofosbuvir/velpatasvir regimen. TRILOGY-3 is a phase 2 open-label trial that evaluated sofosbuvir/velpatasvir/voxilaprevir and sofosbuvir/velpatasvir/voxilaprevir + RBV, both for 12 week durations, as a retreatment regimen in 49 DAA-experienced HCV GT 1 subjects, including 41% of subjects with prior NS5A inhibitor experience. The overall SVR12 rate was 98%; RBV did not improve SVR rates, and baseline RAVs did not reduce SVR rates in this trial.[68] Two phase 2 trials (GS-US-367-1168 and GS-US-367-1169) studied 128 treatment-experienced, including DAA-experienced (79%), HCV GT 1 to 6 subjects, including those with compensated cirrhosis (48%). All subjects were treated with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks. The overall SVR rate was 99% (127/128), with 1 subject experiencing virologic relapse. Baseline RAVs were identified in 60% of the subjects but did not affect the SVR rate in these trials. The regimen was well tolerated in the phase 2 trials and is currently in phase 3 development.[69]

Summary

Treatment of chronic HCV infection has become increasingly well tolerated and effective, with SVR12 rates exceeding 90% in many populations, including those who have historically had limited or no treatment options. However, areas for improvement still remain, in particular for those with HCV GT 3 with cirrhosis, those with decompensated cirrhosis, and those with severe renal disease who are infected with HCV GT 2 or GT 3. Additionally, effective treatment options with high barriers to resistance are needed for retreatment of patients who have failed a prior HCV DAA regimen. With the rapid availability of new HCV DAA treatment regimens and the multiple factors to consider when starting an individual patient on appropriate HCV therapy, the complexity of treatment selection has also increased. Future HCV regimens on the horizon may further address the treatment needs of some difficult-to-treat subgroups and special populations and potentially streamline treatment recommendations.

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Conflicts of Interest

Wendy Carter, Sarah Connelly, and Kimberly Struble are full-time employees of the Food and Drug Administration and have no conflicts to disclose.

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