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Advances in HCV Therapy

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Abstract

Hepatitis C is a devastating illness which has the potential in the majority of cases to lead to significant morbidity and mortality. Worldwide, the number living with chronic hepatitis C approaches 185 million. Up until recently, the regimen of peg-IFN and ribavirin stood as the standard of care and is still commonly used as first line therapy. This is rapidly changing. Direct acting antivirals have altered the landscape drastically. By understanding the genome of the hepatitis C virus, scientists and researchers have been able to exploit its mechanism of transmission by creating inhibitors against several of the nonstructural proteins that are integral to HCV replication and function [NS3/4 protease, NS5A polymerase, and NS5B polymerases (nucleoside and non-nucleoside)]. The previously reported 50%-70% SVR rates achieved with peg-IFN and RBV are no longer the standard of care. Thanks to direct acting antivirals, IFN free as well as "all oral" regimens are being used to treat HCV. In addition to this, ribavirin-free regimens are also available. These highly effective therapies also provide far less side effects and accomplish better results in less time, thus shortening treatment duration significantly. Additionally, even in the notoriously difficult -to-treat populations, results have been promising.

Keywords: Hepatitis C Virus, Direct Acting Antiviral, Treatment, Sustained Virologic Response

1. Introduction

Hepatitis C virus (HCV) infection is a devastating illness, which has the potential in the majority of cases to lead to significant morbidity and mortality. Worldwide, the number living

with chronic HCV approaches 185 million. Until recently, the regimen of pegylated interferon (peg-IFN) and ribavirin (RBV) stood as the standard of care and is still commonly used as first-line therapy in some countries. This is rapidly changing. Direct acting antivirals (DAA) have altered the landscape dramatically. By understanding the genome of the HCV, scientists and researchers have been able to exploit its mechanism of transmission by creating inhibitors against several of the nonstructural proteins that are integral to HCV replication and function. Sustained virological response (SVR), which is commonly defined as a lack of HCV viral detection 12-24 weeks following treatment, with ribavirin and pegylated interferon alone, was marginal but has continued to improve. Despite the improvement, the introduction of DAAs has made the previously reported 50-70% SVR rates fall far short of rates achieved with DAAs.

NS3/4 Protease Inhibitors	NS5A Inhibitors	Nucleos(t)ide NS5B Polymerase Inhibitors	Nonnucleos(t)ide NS5B Polymerase Inhibitors
Boceprevir	Daclatasvir	Mericitabine	*Dasabuvir*
Telaprevir	Elbasvir	*Sofosbuvir*	Deleobuvir
Simeprevir	*Ledipasvir*	VX-135	Lomibuvir
Parotaprevir	*Ombitasvir*		Tegobuvir
Asunaprevir	Samatasvir		ABT-072
Faldaprevir	ACH-2928		BMS-791325
Danoprevir	BMS824393		GS-9669
Grazoprevir	PPI-461		
Sovaprevir	PPI-668		
Vedroprevir	GS-5816		
Vaniprevir			
IDX320			

Legend: Drugs in italics have received FDA approval as of January 2015

Adapted from www.hepatitis.va.gov

Table 1. FDA approved and investigated drugs by mechanism of action

As it currently stands, four classes of DAA exist, which can be categorized according to the protein they inhibit. These four include inhibitors of the NS3/4 protease, NS5A polymerase, and NS5B polymerases (nucleoside and nonnucleoside). The approval of two NS3/4 protease inhibitors, telaprevir (TEL) and boceprevir (BOC), occurred in 2011 and marked the beginning of the age of DAAs. This was followed 2 years later by the approval of sofosbuvir (SOF), a nucleoside NS5B inhibitor, and simeprevir (SIM), an NS3/4 protease inhibitor, further expanded the available treatment options. In 2014, a combination of IFN-free regimen utilizing SOF and an NS5A inhibitor, ledipasvir (LED), was approved. Closely following this, the four-drug combination pack of an NS5A inhibitor, NS3/4A inhibitor, and a nonnucleoside NS5B inhibitor of ombitasvir (OMB), paritaprevir (PARr), and dasabuvir (DAS), respectively, gained Food and Drug Administration (FDA) approval in the United States. In addition to the DAAs in the four-drug combination pack, ritonavir has been added due to its potent inhibition of

CYP3A4, increasing the effect of paritaprevir. Several other agents are currently undergoing late stage clinical trials and are expected to be approved in the near future (Table 1).

2. Epidemiology

In the most recent National Health and Nutrition Examination Survey (NHANES), the estimated prevalence of HCV infection is approximately 3.6 million in the United States alone, with an estimated 2.7 of these having chronic infection. Worldwide, the World Health Organization (WHO) estimates that nearly 150 million people have chronic HCV infection. In both the United States and worldwide, estimates likely fall significantly short given that nearly half of all infected patients have never been tested for HCV. Additionally, the incidence among prisoners and the homeless are not known and in less developed nations are often not recorded [1]. HCV is thought to be the causal factor of up to one-third of cases of cirrhosis worldwide [2, 3].

In a study done by Shepherd *et al.* [4], analysis of positive HCV seroprevalence throughout some of the most populous nations of the world revealed an overall worldly prevalence rate of 2%, or roughly 123 million people. Given the limitations that widespread detection and recording pose, one would expect the actual prevalence to be larger. Individual analysis of many nations including China, Pakistan, and Egypt revealed estimated HCV seroprevalence well above this range. Disease transmission patterns again reveal that the majority of transmission of HCV is thought to be from unscreened blood donation, injection drug use, unsafe therapeutic injection, or other health care-related procedures. As medical practices become safer and blood screening continues to occur, the rates of HCV transmission from injection drug use will become the predominant mode of transmission as it has in developed countries like Australia, England, and the United States. Despite its success in the United States, several barriers to improving the safety of blood transfusions have remained throughout nations across the world [4-6]. As it stands, the WHO's global database estimates that among the 97 of 164 countries that provided data, 89% of donated blood is being screened following basic quality procedures [7].

HCV cirrhosis remains the primary indication for liver transplant (LT) in the United States with over 15,000 patients currently listed on the United Network for Organ Sharing (UNOS) list [8]. In year 2013 alone, over 6,400 patients underwent LT in the United States, increasing steadily from 1,700 in 1988 [9]. The United States leads in amount of deceased donor liver transplantations followed by China, with roughly 2,000 in 2010 [10].

3. Economic impact

As is the case with most newly discovered pharmaceuticals, recently approved DAAs carry with them a financial cost so high that it is a barrier to treatment. At around $1,000 U.S. dollars per pill, a 12-week regimen would run the patient and their insurance provider approximately

$84,000 with other DAA sharing similar price tags. The endeavor of validating coverage depends upon the tangible and the intangible, the objective and subjective, the cold hard science, and the cold hard dollars. Like prior novel pharmaceuticals before them, DAAs will need full support from the respective government in which the regimen is being distributed, as it does in the United States. Governing medical councils such as the FDA, the Health Products and Food Branch (HPFB) of Health Canada, the State Food and Drug Administration (SFDA) in China, and so on, will need to first approve drug regimens and define which population is to receive them.

It is difficult to estimate the exact savings per patient due to the multitude of confounding variables. All things considered, if a patient with HCV progresses naturally without treatment to the point of being considered to have end-stage liver disease. The equivalent of hundreds of thousands of medical dollars will have been spent in order to treat and care for these patients. In addition to the cost savings achieved by no longer needing to treat the manifestations of chronic hepatitis C, the cure of hepatitis C has been also been shown to provide benefits. Beside the improvement in psychological and social well-being, which accompanies cure of HCV, treatment has been shown to decrease and potentially reverse cirrhosis, esophageal varices, and the risk for the development of hepatocellular carcinoma [11-13].

Notably, incomplete treatment, unsuccessful treatment, and reinfection are always possible, particularly in patients with comorbid psychiatric illness, concomitant drug addiction, and poor social support, all known risks factors for contracting HCV [3]. In the long run, this issue should continue to fade in its controversy given that the minimum manufacturing costs for producing direct acting antivirals have been estimated at $100-250 for a 12-week course of treatment once patent expires and production of generic versions are widely available [14]. Additionally, immediate treatment upon detection as opposed to delay in therapy has shown cost-effectiveness [15].

4. Past therapy

Over the past several years, more so recently, treatment options for HCV have exponentially grown. Treatment for HCV began with the FDA approval of interferon (IFN) in 1991, followed by combined IFN and RBV in 1998, and later with peg-IFN in 2001. The regimen of peg-IFN and RBV once stood as the standard of care, and still does in many nations, until recently. DAAs, which target nonstructural proteins involved in replication and infection of HCV, were first approved in 2011.

Peg-IFN and RBV historically have been shown to result in SVR rates of 75% in patients with genotypes 2 or 3, but only of 40% in patients with genotype 1 [16]. The duration of therapy often depended on both patient's genotype and their response to therapy as measured by HCV RNA viral load following initiation of treatment [17]. In one-third of all patients being treated with peg-IFN and RBV, adverse side effects were noted. These ranged from an influenza-like illness, characterized by fatigue, headache, fever, and rigors as well as complaints of depression, irritability, or insomnia. In addition to the side effects, therapy with peg-IFN was a tedious

experience. Treatment often included weekly subcutaneous injections of peg-IFN in addition to daily oral RBV for up to 48 weeks. In addition to this, patients required at least monthly appointments for the first 12 weeks for monitoring of side effects and blood work, including HCV viral load monitoring. The tedious schedule and weekly subcutaneous injections lead many to either not enroll for therapy or undergo incomplete treatment.

As it stands now, the time of weekly injections and unfavorable side effects are gone. In 2014, new IFN-free regimens became available. The previous peg-IFN and RBV therapy or even triple therapy involving TEL or BOC is quickly becoming extinct. In 2015 onward, IFN-containing regimens will be replaced by all-oral, IFN-free therapies. Additionally, RBV-free regimens are also becoming widely available, and RBV will likely go the way of peg-IFN due to its unfavorable side effect of anemia.

5. Direct acting antiviral therapy

As noted thus far, the groundbreaking development of DAAs has appeared to instantaneous change a bleak and dismal diagnosis to one filled with hope and promise. HCV seems to be paralleling HIV in that it was once considered a death sentence where treatment was harsh and limited but has now changed to something treatable with a pill. Additionally, one can now expect to live a near normal lifespan and be contributors to society.

The genome of HCV is now well understood, and because of this, scientists have been able create inhibitors against components of the genome integral to HCV replication and function. As it currently stands, four classes of DAAs exist and include the NS3/4 protease inhibitors, NS5A polymerase inhibitors, and the NS5B polymerases (nucleoside and nonnucleoside) inhibitors. Starting with protease inhibitors in 2011, BOC and TEL changed the game and raised SVR to impressive levels in treatment-naive patients. Shortly after, SOF, a nucleoside NS5B inhibitor, and SIM, another NS3/4 protease inhibitor, were approved and progress soared. It was not long before the old regimen of peg-IFN was being disposed of for more convenient and more tolerable agents. In the past months, additional agents have been approved and include LED, OMB, PARr, and DAS. Many more are under investigation and will likely be approved by the time of this publication.

The treatment of HCV centers on achieving SVR because if one can achieve this then life expectancy approaches near normal [18]. Without a detectable HCV viral load, cirrhosis is not expected to be occurring, and therefore neither are the complications thereof. Historically, achieving SVR in unique patient populations has proven difficult. Additionally, patients with certain factors often did not tolerate treatment well. In these populations, treatment was not approved, i.e., post liver transplant HCV patients. Genotypic analysis has also helped to identify unique populations. It has been established that some strains of HCV appear to possess an innate resistance to peg-IFN and RBV. Further exploration into genotypic and polymorphic variation and its effect on treatment response is needed, particularly now that these new agents with different mechanisms of action than peg-IFN and RBV are being utilized.

5.1. Genotype specific

HCV is classified into 11 genotypes with the first 6 of these garnering the majority of attention. Interestingly, various genotypes possess a geographic predominance [19] (Table 2).

Genotype	Geographic distribution
1	United States, Europe, Japan
2	Mediterranean, Europe, Japan, North America
3	Southeast Asia, Europe, United States
4	Egypt, North Africa, sub-Saharan Africa, Middle East
5	South Africa
6-11	China, Korea, Taiwan, Southeast Asia

Table 2. HCV genotype geographic distribution

Genotype 1 is the most prevalent genotype in the world and until recently had been the most difficult genotype to treat due to its poor SVR rates in response to peg-IFN and RBV. Treatment over the years has evolved significantly and the newest available guidelines support the use of the SOF/LED combination or the OMB/PARr/DAS/RBV combination [20-27]. Alternatively, data also indicate that use of SOF, SIM with or without RBV, achieved acceptable rates of SVR and can also be considered for use [28]. In patients with genotype 1 HCV infection, new SVR targets are now at greater than 90%. Newer therapies will need to measure up to these results. New agents remain under study, but preliminary results have been as impressive as the above regimens, and thus the market for treatment of genotype 1 infection will be saturated before we know it [29, 30] (Table 3).

Genotype 2 is found in clusters in the Mediterranean region and has historically responded well to the previous standard of peg-IFN and RBV. Genotype 3, now becoming the most difficult genotype to treat, has the unique characteristic of being associated with intravenous drug use. Recent studies using the newer DAAs show increased rates of SVR. Current recommendations for treatment suggest ample success is possible by utilizing a SOF and RBV regimen [31-36]. Building on excellent results of a phase II trial, an ongoing phase III trial is pending and expected to show widespread success with the use of daclatasvir (DAC) in combination with SOF [37, 38]. DAC, an NS5A inhibitor, has shown similar promising results throughout all genotypes as expected given its pan-genotypic treatment effect. Other promising regimens include SOF/LED combination, as well as GS-5816, a pan-genotypic NS5A inhibitor in combination with RBV [39, 40] (Table 4).

Genotype 4 is found mostly in Egypt, the Middle East, and northern Africa. Although rare in the United States, in Egypt, the prevalence of HCV is upwards of 15% and thus remains an important research focus. Similarly, genotypes 5 and 6 are rare in the United States and are more frequently found in southern Africa, Southeast Asia, China, and Korea. Given the geographic distribution, few genotype 4-6 patients have been enrolled in clinical trials. More

research is needed, but SOF-based regimens are likely to be significantly effective in the meantime [31, 41-46] (Table 5).

Trial	Phase	n	Regimen	SVR	Comments
ION-1 [20]	III	865	SOF/LED ± RBV for 12 or 24 wks	>97%	Included patients with compensated cirrhosis
ION-2 [20]	III	440	SOF/LED ± RBV for 12 or 24 wks	>94%	Previously treated patients with and without cirrhosis. Lower SVR was observed in the 12-week group without RBV.
ION-3 [21]	III	647	SOF/LED ± RBV for 8 or 12 wks	>93%	Included patients with compensated cirrhosis in 12 week arm
SAPPHIRE-I [22]	III	631	OMB/PARr/DAS + RBV for 12 wks	>95%	Absence of cirrhosis required
SAPPHIRE-II [25]	III	297	OMB/PARr/DAS + RBV for 12 wks	>96%	Previously treated patients without cirrhosis. SVR similar regardless of previously treatment failure.
PEARL-III [23]	III	305	OMB/PARr/DAS ± RBV for 12 wks	>90%	G-1a patients
PEARL-IV [23]	III	419	OMB/PARr/DAS ± RBV for 12 wks	>99%	G-1b patients
TURQUOISE-II [24]	III	380	OMB/PARr/DAS + RBV for 12 or 24 wks	>92%	Patients with compensated cirrhosis
COSMOS [28]	II	167	SOF/SIM ± RBV for 12 or 24 wks	>90%	Extending treatment and RBV did not significantly improve SVR, phase III trial ongoing(OPTIMIST)
SIRIUS [27]	II	155	SOF/LED for 24 wks or SOF/LED + RBV for 12 wks	>96%	Previously treated patients with and without cirrhosis. 12 week course proved as effective.
C-WORHTY [26]	II	253	GRZ/ELB ± RBV for 12 or 18 wks	>90%	Previously treated and untreated with and without cirrhosis

Legend: Wks: week; GRZ: grazoprevir; ELB: elbasvir

Table 3. Results of DAA treatment in genotype 1 patients

Trial	Phase	n	Regimen	SVR	Comments
FISSION [31]	III	499	SOF + RBV for 12 wks	97%	Compared to previous standard, SOF greatly improved SVR rates from 78% to 97%
POSITRON [32]	III	278	SOF + RBV for 12 wks vs placebo	78%	SVR was higher for G-2(93%) vs G3(61%)

Trial	Phase	n	Regimen	SVR	Comments
VALENCE [33]	III	419	SOF + RBV for 12 or 24 wks	>78%	G-2 was treated for 12 wk and G-3 was treated for 24 wks in patients with and without cirrhosis who were and were not previously treated. Lowest SVR(78%) was noted in the previously treated, cirrhotic genotype 3 patients.
FUSION [32]	III	201	SOF + RBV for 12 or 16 wks	>86%	Previously treated patients with and without cirrhosis.
LONESTAR II [34]	II	47	SOF + RBV + peg-IFN for 12 wks	>96%	Previously treated patients with and without cirrhosis
A144040 [37]	II	44	DAC + SOF ± RBV for 24 wks	>88%	
PROTON [35]	II	25	SOF + RBV + peg-IFN for 12 wks	92%	
ELECTRON [36]	II	50	SOF + RBV ± peg-IFN for 12 wks	100%	Among the SOF + RBV arms of the study SVR was high, the SOF only group reported an SVR of 60%

Legend: Wks: week; DAC: daclatasvir

Table 4. Results of DAA treatment in genotypes 2 and 3 patients

Trial	Phase	n	Regimen	SVR	Comments
NEUTRINO [31]	III	327*	SOF + RBV + peg-IFN for 12 wks	96%	Patients with genotypes 1, 4, 5, and 6. Of these 27/28 genotype 4 patients and 7/7 genotype 5 and 6 achieved SVR.
Egypt Ancestry Trial [41]	II	60	SOF + RBV for 12 or 24 wks	>79%	SVR was lowest in the 12-wk, treatment naïve group.
RESTORE [42]	III	107	SIM + RBV + peg-IFN for 12 wks	>65%	SVR of 83% in the treatment naïve group, 40% in the prior null responders
PEARL I [43, 44]	II	86	OMB/PARr ± RBV for 12 wks	>91%	Preliminary data, patients in the RBV group achieved 100% SVR

Trial	Phase	*n*	Regimen	SVR	Comments
SYNERGY [45]	II	21	LED/SOF for 12 wks	95%	Preliminary data, included previously treated patients
ATOMIC [46]	II	316	SOF + RBV + peg-IFN for 12 or 24 wks	>82%	Patients with genotypes 1, 4, 5 and 6; 9/11 genotype 4 and 5/5 genotype 6 achieved SVR

Legend:*Of the 327, only 28 patients were genotype 4; Wks: week

Table 5. Results of DAA treatment in genotype 4, 5 and 6 patients

6. Unique populations

Large phase III trials convincingly show favorable SVR in patients who are naive to treatment, noncirrhotic, and in non-HIV coinfected. However, what about patients who do not fit into these categories? Furthermore, concern for side effect profile, inadequate practitioner training, and concern for drug-drug interaction have led to avoidance in all but treatment-naive and otherwise healthy patients.

In addition to the unique groups of patients described below, other factors should also be taken into consideration as they can complicate the decision as to which treatment should be initiated. These include patients with renal failure, heart failure, and comorbid psychiatric illness to name a few. The medical comorbidities of each individual is a hornet's nest of potential failure, and as such, each case embarked upon should be done so with careful consideration of all coexisting medical and psychological conditions. To ensure of this, it is helpful to have a trained multidisciplinary team made up of physicians, pharmacists, nurses, psychologists, and social workers. Aside from making medication dose adjustments when required, current guidelines recommend that in the presence of complex comorbid medical conditions, treatment of HCV be initiated and managed by a hepatologist and potentially at a medical center affiliated with liver transplantation [47].

6.1. Treatment experienced

Patients who have been previously treated pose perhaps one of the most common dilemmas that practitioners face. Often times, patients get retreated due to initial therapeutic failure (typically to peg-IFN and RBV) or HCV relapse. Patients may be presenting for retreatment following previous partial treatment or after being lost to follow-up. Rarely, patients can become reinfected with HCV. In all scenarios, therapy with new HCV drug regimens should be offered.

Initial studies with TEL, BOC, and SIM showed encouraging results. In the REALIZE trial, nonresponders, partial responders, or those who have suffered a relapse were randomized

into three treatment groups separated by treatment duration. An SVR rate of 66% was achieved in the 12-week treatment arm of TEL, peg-IFN, and RBV [48]. Similarly, BOC in combination peg-IFN and RBV was able to achieve rates of SVR of 63% overall, however only 38% in prior nonresponders [49]. Larger trials and trials utilizing SIM showed similar results [50-53]. In general, all studies reported adverse side effects of severe anemia, requiring treatment discontinuation, dose reduction, or transfusion. Given the poor response of prior null responders, treatment utilizing TEL, BOC, or SIM in combination with peg-IFN and ribavirin is not recommended in the treatment experienced population.

Several promising trials evaluating the therapeutic benefit of newer DAAs have been reported with high overall SVRs, few side effects, and minimal drug interactions. (Tables 3-5). Based on these trials, recommendations regarding appropriate therapy as tailored to the genotype have been made. In general, genotype 1 patients have several options as convincing results as to effectiveness has been produced with either SOF/LED, SOF/SIM, or the four-drug combination of PARr/OMB/DAS/RBV. For those with genotype 2 or 3, reassuring data from the LONE-STAR-2 trial that achieved SVR rates of 83-96% in these patients confirmed that a 12-week regimen of SOF, RBV, and peg-IFN be used [34]. For those not eligible for peg-IFN, SVRs of 80-90% were still achievable with SOF and RBV alone [32, 33]. In genotype 4 patients, options include SOF/LED, SOF/RBV with or without peg-IFN, or the four-drug combination of PARr/OMB/DAS/RBV. As with the treatment-naive patients, genotype 5 or 6 has few reported data, but an SOF-based regimen will likely be efficacious.

6.2. Decompensated cirrhosis

Cirrhosis, regardless of its level of compensation, is known to result in a decreased SVR in patients being treated for HCV. On decompensation with the development of ascites, variceal hemorrhage, encephalopathy, or coagulopathy, the probability of survival is only 50% at 5 years, with a median survival of only 2 years [54, 55]. Thus, it remains imperative to provide rapid and effective treatment for HCV.

A meta-analysis done by Vierling *et al*. [56] examined several phase III clinical trials of patients undergoing HCV treatment with biopsy proven cirrhosis. In the trials of patients receiving the standard therapy of peg-IFN and RBV, an overall SVR of 20% was found. In 2011, riding the momentum of improved SVR in noncirrhotic patients receiving triple therapy, BOC, TEL, and SIM were given in combination with peg-IFN and RBV, and the rate of SVR increased significantly to 55% and 74%, respectively, in this previously dismal population [53, 56]. Improvement in SVR was not without its drawbacks. In the BOC- and TEL-treated groups, significant side effects of anemia and diarrhea were noted. Slightly less severe side effects of flulike illness and pruritus were noted in those treated with SIM; however, significant resistance was found in genotype 1A patients who possessed a specific genetic polymorphism known as the Q80K mutation. A screening test for detection of this mutation is available, and given that nearly 50% of United States and 20% of European patients had the mutation at baseline, testing should be conducted prior to treatment with SIM [57].

Following on the success of a trial conducted by Gane *et al*. [58], which showed an SVR in 9 out of 9 patients with decompensated cirrhosis treated with SOF, LED, and RBV, the SOLAR-1

trial was conducted. This trial was a multicenter, randomized trial of 108 patients with genotypes 1 and 4 HCV whom also had Child-Pugh class B or C cirrhosis. Excluding 6 patients who underwent eventual liver transplant, an SVR of 87% and 89% was attained in the 12- and 24-week treatment groups, respectively. Given the larger chance of adverse events observed in the 24-week group, consensus guidelines for treating genotypes 1 and 4 patients with decompensated cirrhosis support a 12-week course of SOF, LED, and RBV [47]. Most importantly, the patients with virologic response had significant improvement in liver function, including improvements in bilirubin, albumin, modified end-stage liver disease (MELD) scores, and Child-Pugh scores. These guidelines recommend that for genotypes 2 and 3, daily SOF and RBV should be utilized up to 48 weeks for treatment. These recommendations are based on sparse data showing an achieved SVR in 10 of 11 patients [59]. Further data is needed in this group and is expected to change guidelines further. Preliminary data reported on the use of SOF, LED, and RBV for 12 weeks in genotype 3 patients showed favorable results with an SVR being achieved in all 26 patients treated [60].

Further research is needed in this group, including studies evaluating larger groups of patients to delineate a specific regimen. As it stands, similar to other unique populations, it appears that second-generation agents such as SOF, LED, and the like provide a superior benefit to first-generation protease inhibitors like SIM, TEL, and BOC. In addition to the pan-genomic action, improved dosing regimens, less drug-drug interactions, and more tolerable side effect profiles make them a first choice in patients with decompensated cirrhosis regardless of liver transplant candidacy.

6.3. HIV coinfected

HIV-infected individuals with concomitant hepatitis C are known to have an increased morbidity and mortality [61]. Following the development of highly active antiretroviral therapy (HAART), there has been an ever-increasing percentage of HIV-infected patients who are dying from liver disease. In HIV-infected patients, death from liver disease remains far more prevalent than death attributable to HIV-related complications [62, 63].

Historically, having coinfection with HIV also leads to poor responses to peg-IFN and RBV therapy [64, 65]. Additionally, coinfection with HIV also lead to increased risk for progression to cirrhosis [66]. On a molecular level, it has been postulated that the higher viral load of HCV RNA noted in this population is secondary to both increased replication of HCV RNA by HIV proteins as well as a generalized state of immunodeficiency [67, 68].

Up until recently, treating patients with coinfection of HIV was felt to be difficult secondary to the historically poorer responses to peg-IFN and RBV. Recently, however, concern regarding potential drug-drug interactions has existed and has lead to practitioner trepidation [69, 70]. This has fortunately not panned out, and several large trials have shown excellent results in treatment of the HCV/HIV coinfected.

With protease inhibitors approved first, trials utilizing a triple therapy of either TEL or BOC in combination with peg-IFN and RBV were conducted. Sulkowski *et al.* [71] treated 62 coinfected genotype 1 patients with TEL, peg-IFN, and RBV achieved an SVR of 74%. In another

study, using triple therapy with BOC in combination with peg-IFN and RBV, an SVR of 63% was attained; however, significant side effects leading to dropout in 12 of 65 patients occurred. This dropout continues to be a concern and is thought to be secondary to side effects, high pill burden, and pharmacokinetic interactions between HCV NS3/4A protease inhibitors and antiretroviral drugs [72, 73].

Following on the success of first-generation DAAs, trials utilizing SOF were later conducted. In a study of genotype 1 patients, Osinusi *et al.* [74] treated 50 HCV and HIV coinfected patients with 12 weeks of SOF and LED. Grouping based on HAART naive versus on HAART showed no difference in the 100% SVR rates achieved in both groups. No adverse events or discontinuations were noted during the treatment period. Sulkowski *et al.* [75] was able to achieve an SVR of 67-88% based on genotype following a 12- to 24-week course of SOF and RBV. Of note, this approach was void of significant drug-drug interactions. In an even larger trial conducted by Molina *et al.* [76], 275 patients with genotypes 1-4 HCV underwent treatment with a 12-week course of SOF and RBV. The overall SVR rate achieved was 85% in genotype 1, 88% in genotype 2, 89% in genotype 3, and 84% in patients with genotype 4. Given the results of these trials, an SOF-based regimen, free of peg-IFN, is recommended; however, with new drug regimens being approved, further studies and head-to-head trials will need to be conducted in order to truly determine the best choice for these select patients.

6.4. Recurrence after liver transplant

Graft failure and fibrosis remain a feared complications among patients transplanted for HCV. Invariably, HCV recurs in all patients following transplantation. Similar to the pretransplant state, patients with HCV progress to fibrosis and eventual decompensation of the transplanted liver. Patients who undergo liver transplantation as a whole have been shown to have higher rates of mortality for this reason [77-79]. Routine monitoring has gone far to anticipate these changes; however, treatment needs continued improvement. Until recently, treatment with peg-IFN and RBV was only marginally effective, and use in this population was off-label. With the newly discovered DAAs, great promise for treatment exists. In addition to the superb ability to achieve SVR, DAAs offer favorable side effect profiles with manageable drug interactions with common immunosuppressive regimens. Some of the DAAs have been shown to do this better than others.

Complicating factors that must be discussed in this patient population include donor and recipient variables. Independent of the treatment regimen, certain characteristics have been shown in large retrospective analysis to negatively impact progression to fibrosis and cirrhosis following LT. The presence of advanced donor age or steatosis as well as specific genetic polymorphisms in both the donor and the recipient can lead to advanced progression of fibrosis [80-83]. Factors such as living vs. deceased donor, human leukocyte antigen (HLA) matching, and HCV positive donor status have not been shown to reliably contribute to fibrosis progression [84, 85]. Within the context of HCV-related liver transplantation, several studies have also attempted to identify specific allelic variants that may contribute to either poor response to standard antiviral therapy or a more rapid progression of fibrosis [86, 87]. Further studies are needed to confirm these, however, and as it stands due to the limited supply, the

allocation of available livers for transplant based on the presence of nucleotide polymorphisms is not practiced (Table 6).

Donor Factors	Recipient Factors
Age >50 years	Genotype 1B
Liver steatosis >30%	IL28B Genotype CT and TT
IL28B Genotype CT and TT	
Lack of DDX58 polymorphism	

Table 6. Factors leading to worse outcomes following liver transplantation

Currently, three treatment strategies for management of HCV in the transplant setting are being used. The first strategy involves treatment of patients currently listed for transplantation. Until recently, the barrier with this strategy has been that with peg-IFN, RBV and the early DAAs patients often either do not tolerate therapy or do not achieve SVR [88]. The second strategy that is not being used thus far involves treating HCV recurrence immediately following liver transplantation. Whether or not this method of treatment increases in popularity will be determined by the tolerability and side effects of the new DAAs. The third and most commonly used strategy involves initiating treatment after several months following transplantation and noted progression of HCV.

Several trials have evaluated the effectiveness of using peg-IFN and RBV in order to treat HCV recurrence in patients following LT. The results have not been favorable, and side effects, particularly anemia, have posed barriers to treatment completion. Overall SVR, in patients with minimal fibrosis, following 48 weeks of therapy was only 48% [89]. Follow-up studies have had even less favorable results [90]. Therefore, peg-IFN and RBV alone is not recommended in this treatment group.

In the largest series evaluating the use of TEL and BOC for the treatment of HCV recurrence following liver transplantation, Burton et al. [91] successfully treated 81 patients with genotype 1 HCV and achieved an SVR at 12 weeks of 63%. Despite its success, TEL and BOC in combination with peg-IFN and RBV led to severe side effects of anemia requiring a transfusion in nearly 50% of patients. Additionally, close monitoring of immunosuppressant drug levels was required, and frequent dose adjustments were needed. Given these results, the use of BOC and TEL are not recommended unless newer, better-tolerated agents are unavailable.

Recent trials report favorable tolerability and highly effective results with the use of new DAAs. In a trial evaluating 40 patients treated with RBV and SOF, an SVR12 of 70% was achieved [92]. Slightly better results were achieved in the HCV-TARGET consortium, which evaluated 189 patients being treated with SOF-based regimens. Overall, SVR among the groups ranged from 69% to 88%. Additionally, SOF and SIM regimens achieved SVR12 of 80-88% depending if RBV was used [93]. The utilization of SOB in combination with LED is also being looked at and has shown that in patients with compensated disease and minimal cirrhosis, a highly favorable SVR12 of 96% could be attained. This regimen is also appealing

as it only required 12 weeks of therapy [94]. Current guidelines put in place by the AASLD-ISDA recommend treatment of genotype 1 infection with combination SOF and SIM. For genotype 2 or 3, SOF or RBV alone is recommended [47]. These recommendations are likely subject to change given approval of LED as well as favorable results of a trial looking at ritonavir-boosted paritaprevir, coformulated with ombitasvir, plus dasabuvir [95]. The treatment of post-LT patients with more advanced cirrhosis (Child-Pugh B or C) continues to require further study; however, preliminary results reveal that even in this highly difficult-to-treat group, an SVR of 81% could be achieved [94]. Other regimens continue to be under investigation at this time.

It is anticipated that all-oral DAA regimens will be both highly effective as well as highly tolerated in the liver transplant setting. Continued research evaluating safety profiles of these medications should be done, but in the meantime, given the amount of evidence currently available and in accordance with current guidelines, the initiation of a sofosbuvir-based regimen in this patient population is highly recommended.

7. Future therapy

As alluded to in the sections above, DAA research is producing large quantities of favorable data, particularly in genotypes prevalent in Europe and the United States. Numerous clinical trials have been completed. More trials are ongoing or are recruiting. Naturally, head-to-head trials are needed to differentiate between many of the already known successful regimens, but few will agree to this in the short term. Future research should aim to improve the currently available classes of HCV drugs with the goal of limiting significant side effects. Specifically, we hope that all newly developed NS3-4A protease inhibitors, nucleoside/nucleotide analogues, nonnucleoside inhibitors of HCV NS5B, and NS5A inhibitors share a similar high-potency, pan-genotypic antiviral activity, and high barrier to resistance. In the distant future, perhaps DAAs will have lost their utility as research on vaccination continues [96].

8. Summary

Therapy for HCV has seemed to exponentially grow over the past 4 years. Because of DAAs, IFN-free as well as all-oral regimens are being used to treat HCV. In addition to this, ribavirin-free regimens are also available. Thus far, these highly effective therapies have proven to provide fewer side effects and achieve better results, all the while in less time. Hope for cure and eradication remains paramount and is now achievable. With appropriate allocation of resources, physician training, and available treatment, the cure of HCV is possible. Doing so will drastically decrease overall health care costs, improve quality of life, and decrease the number of liver transplants needed.

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