Current Therapy of Chronic Hepatitis C Virus in Treatment-Naive Patients

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Alhareth AlJuboori, Satinder Kaur, and Veysel Tahan

4.1 Introduction

Hepatitis C virus (HCV) is one of the most commonly transmitted blood-borne diseases in the United States, with chronic cases ranging from 2.7 to 3.9 million in the United States and 130–170 million worldwide [1]. As reported by Denniston et al., the actual number of cases in the United States is underestimated because the survey precluded high-risk populations such as prisoners and homeless population [2]. Roughly 95% of the worlds and 50% of the United States' HCV-infected population are unaware of their infectious status [3]. It can be transmitted by blood transfusions, intravenous drug administration, intranasal drug administration, sexual intercourse, and vertical transmission [1].

The progression from acute hepatitis C to chronic HCV infection is poorly defined. About 15–45% will clear an acute infection with estimates of time to clearance ranging from 1 to 2 weeks up to 1–3 years [1, 4]. Of the patients who fail to clear they go on to develop chronic HCV and after 2–3 decades of untreated chronic HCV, 10–20% of these patients are expected to develop cirrhosis [4]. HCV is the leading case of chronic liver disease, cirrhosis, and hepatocellular carcinoma, and the main indication for liver transplantation in the Western countries [5]. Chronic HCV is a major public health concern with total healthcare costs associated with HCV disease and its complications, excluding treatment expenses, estimated to be $6.5 billion in 2011, with a projected increase to $9.1 billion by 2024 [6].

A. AlJuboori · V. Tahan (✉)
Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Missouri School of Medicine, Columbia, MO, USA
e-mail: Aljubooria@health.missouri.edu; tahanv@health.missouri.edu

S. Kaur
Department of Internal Medicine, VA Sierra Nevada Health Care System, University of Nevada School of Medicine, Reno, NV, USA
e-mail: satinderk@med.unr.edu

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Since early diagnosis and revolutionary advancements in current treatment options can prevent cirrhosis and HCC, the CDC recommends a general screening strategy with a one-time testing without prior ascertainment of HCV risk for baby boomers—persons born during 1945–1965 [7].

Treatment of chronic HCV with the new direct-acting antivirals (DAAs) has shown increased SVR rates, simpler regimens, and less severe side effect profiles, making it ideal to start treatment earlier. We will discuss current available chronic hepatitis C treatment regimens with DAAs, and the supporting trials from which the recommendations are made.

4.2 Hepatitis C Virus and Its Proteins

Hepatitis C virus was first identified by Choo et al. in 1989, as an enveloped single-stranded RNA virus, belonging to Flaviviridae family [8]. The virus can circulate through the human body but has a strong affinity towards the liver and invades the hepatocytes by endocytosis. The hepatitis C virus contains a single-stranded RNA that is translated to a large polyprotein that cleaves into ten mature proteins using either host or viral proteases inside endoplasmic reticulum, yielding structural (core, E1, E2, and p7) and nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) [9].

Structural proteins are involved in forming viral particles. HCV core is the viral nucleocapsid protein, and E1/E2 are glycosylated envelope glycoproteins that surround the viral particles [9]. The structural proteins are separated from the nonstructural proteins by the short membrane peptide p7 [9].

Nonstructural proteins are components of the replication complex. NS2 is a non-glycosylated membrane protein that participates in proteolytic cleavage at the NS2-NS3 junction [9]. NS3 consists of the N-terminal HCV serine protease and the C-terminal RNA helicase domain [9]. NS3 proteinase domain associates with NS4A and is a cofactor for NS3 protease which plays a critical role in HCV processing by cleaving downstream of NS3 at four sites (between NS3/NS4A, NS4A/NS4B, NS4B/NS5A, NS5A/NS5B) [10]. NS4B is an integral membrane protein that cotranslationally associates with the endoplasmic reticulum (ER) membrane inducing the formation of a seemingly ER-derived membranous web that harbors all HCV structural and nonstructural proteins as well as replicating viral RNA [9, 11]. NS5A binds the viral RNA and various host factors in close proximity to HCV core and lipid droplets [12]. NS5A protein lacks enzymatic activity, and appears to have multiple roles in establishing the replication complex, in viral assembly, and in inhibiting apoptosis. NS5A is also involved in mediating resistance of the hepatitis C virus to the action of interferon [13]. NS5B is the RNA-dependent RNA polymerase [12].

4.3 Hepatitis C Genotyping

HCV is a very heterogeneous virus, and has substantial genetic variability. Currently there are seven different genotypes (GT) of HCV 1–7 [1]. HCV genotypes differ from each other at 30–35% of nucleotide sites, and each GT is further classified as

67 confirmed and 20 provisional subtypes [14]. The most commonly demonstrated subtypes are GT1a and GT1b.

Globally, GT1 is estimated to account for 46.2%, GT2 9.1%, GT3 30.1%, GT4 8.3%, GT5 <1%, and GT6 5.4% [15]. In the United States, approximately 70% of chronic HCV infections are caused by hepatitis C GT1, 15–20% by GT2, 10–12% GT3, 1% GT4, and less than 1% GT5 or -6 [16].

Over one-third of GT1 cases are located in East Asia, whereas three-quarters of the global estimate of GT3 cases occur in south Asia [15]. GT2 and GT6 were seen mostly in East Asia, GT4 in North Africa and Middle Eastern region, and the majority of GT5 cases occur in Southern and Eastern sub-Saharan Africa [15].

4.4 Historical Interferon Era in HCV Therapy

Before advancements in chronic hepatitis C therapy the standard of care for treatment consisted of pegylated interferon (PegIFN) and weight-based ribavirin. The regimen depended on genotype, viral load at baseline, and treatment, with the duration of treatment being driven by HCV RNA quantification and sustained virologic response (SVR). For GT1, GT4, GT5, or GT6 the recommended duration of treatment was 48 weeks, and for GT2 and GT3 it was 24 weeks. These recommendations were based on data that supported GT2 and GT3 being more responsive to this regimen with SVRs of 80%, compared to SVR rates of 40–50% with GT1 [17].

For GT1 early virological response was determined at week 12 in hopes of not overtreating patients with low changes of achieving SVR. Viral load was measured and if it dropped ≥ 2 $\log_{10}$ from baseline with or without detection of the HCV RNA treatment was continued for 48 weeks. If HCV RNA continued to be detectable at week 24 then treatment was stopped as the likelihood of an SVR was virtually zero, but it could be continued with the aim to slow liver disease progression in patients with a severe prognosis [18]. For GT2 or GT3, no monitoring of HCV RNA during therapy was recommended because clear majority became HCV RNA negative early in treatment, but it was measured at the end of therapy to assess whether the virologic response was sustained [19]. As more data and research became available it was determined that regimens could be shortened to 24 weeks for GT1 and 16 weeks for GT2 if the patient showed rapid virological response (RVR) which was defined as an undetectable viral load at week 4 [18, 19].

In general, the concluded SVR response using these regimens was limited and the adverse effect profile was intolerable due to hematological toxicities, psychiatric disruptions, fatigue, and flu-like symptoms.

4.5 The Four Classes of Direct-Acting Antivirals (DAAs)

The four classes of DAAs include NS3/4A protease inhibitors, NS5A inhibitors, non-nucleoside NS5B polymerase inhibitors, and nucleoside and nucleotide NS5B polymerase inhibitors.

NS3/4A protease inhibitors—prevent cleavage of the nonstructural proteins and inhibit the ability of the virus to evade the immune response [20]. Current protease inhibitors include simeprevir, paritaprevir, and grazoprevir which have been approved in combination with NS5A/B inhibitors for GT 1 and/or 4 disease [1].

The first breakthrough in direct-acting antiviral era was in 2011 when telaprevir and boceprevir were approved to be used to treat chronic hepatitis C. Both are considered first-generation NS3/4A protease inhibitor, and were used in triple therapy along with PegIFN/ribavirin. The SVR rates showed improvement with triple therapy and in patients with GT1 SVR rate went from 50% to greater than 70% [20]. However, along with the improved SVR rates there was also a higher frequency of adverse events noted. Boceprevir triple therapy is associated with increased risk of neutropenia, dysgeusia, anemia, thrombocytopenia, and telaprevir triple therapy is associated with increased frequency of anemia, pruritus, and rash in up to 50% of patients, and associated with severe events in up to 5–10% of patients [20, 21].

The second class of the first generation of protease inhibitor was simeprevir with activity against genotypes 1, 2, 4, 5, and 6. Along with PegIFN/ribavirin, simeprevir was used for 12 weeks with subsequent additional 12–36 weeks of PegIFN/ribavirin depending on patient's treatment history. This regimen increased SVR rates from 50% up to almost 80%, except in GT1a population with Q80K resistance-associated substitution (RAS), in which case patients were seen to have SVR12 rates of 46.7% [20, 22].

NS5A inhibitors—work by inhibiting hyperphosphorylation, which is required for viral replication, and binding to NS5A domain 1 and preventing RNA binding without affecting NS5A dimerization [23]. Examples include ledipasvir, daclatasvir, elbasvir, ombitasvir, and velpatasvir [1]. Daclatasvir was coupled with PegIFN/ribavirin for 24 weeks for genotype 4 populations in Europe and showed evidence of improving SVR rates [24].

Polymerase inhibitors interfere with viral replication by binding to the NS5B RNA-dependent RNA polymerase. There are two types of polymerase inhibitors—nucleoside and non-nucleoside inhibitors.

Nucleoside analogue polymerase inhibitors—require conversion to an active triphosphate form and once active it inhibits the RdRp active site and causes chain termination [20]. Sofosbuvir was the first approved IFN free therapy for GT2 or -3, but research showed that it was not as successful in those with GT1 [1].

Non-nucleoside analogue polymerase inhibitors—suppress RdRp activity by binding to several discrete sites on HCV polymerase in a noncompetitive fashion to arrest HCV viral replication [20]. This class is only active against GT1. Dasabuvir is an example of this class.

4.6 Indications and Goals of Therapy

Major goal of therapy is to prevent HCV-related complications including advanced fibrosis, cirrhosis, and extrahepatic complications. Extrahepatic complications of chronic hepatitis C include diabetes mellitus, cardiovascular disease, lymphomas,

and renal disease [25]. Treatment-naive patients represent a group of patients who are infected with chronic hepatitis C without any previous experience with treatment including interferon, ribavirin, or any direct-acting antiviral. Treatment-experienced patients are those who previously underwent treatment with one of the above agents and failed to cure HCV infection. Both groups need to be treated regardless of their liver status. All patients without cirrhosis, but significant or advanced fibrosis (METAVIR score F2-F3), need to be considered for treatment without delay [26]. Extrahepatic complications are considered an indication for initiating therapy including HCV related nephropathy, cryoglobulinemia, B-cell lymphomas, and vasculitis [25]. Treatment also needs to be considered in patients with coinfection with HIV or hepatitis B to prevent further progression of hepatic fibrosis [7]. For decompensated cirrhosis with high MELD score >18–20, treatment needs to be considered after liver transplantation due to the risk of treatment failure and lack of evidence of significant liver function improvement and eventual delisting [7, 26]. For all liver-transplanted patients, treatment is indicated after transplant. IV drug abusers, incarcerated persons, and patients on hemodialysis also need to be treated, as it has been shown that treating this population will reduce disease transmission in the future [7, 26].

4.7 Pretreatment Patient's Evaluation

The most pivotal assessment for a patient with chronic hepatitis C is to identify patient's fibrosis stage as it has a great impact on patient's prognosis and disease outcome. Early detection and prevention is the most effective approach to substantially impact the prognosis as treatment can be started earlier, and the biomarkers could also improve early HCC detection.

Liver biopsy is the gold standard for fibrosis staging; however limiting factors include sampling error and observer variability. Also of note is the possibility of discordance between fibrosis stages in the different lobes. Given the invasive nature of the procedure minor and rare major complication can occur, and for that reason noninvasive methods should be used for initial fibrosis assessment.

Noninvasive methods include both serum biomarkers and imaging techniques. Noninvasive imaging techniques however outperform the serum-scoring systems but most biomarkers are accurate for advanced-stage disease.

Serum biomarkers are categorized as either direct or indirect. Indirect markers include bilirubin, aminotransferase levels, gamma-glutamyl transpeptidase, prothrombin time, albumin, and platelet count. These markers are used in algorithms to form the following tests: APRI test, FIB-4, FibroSure, and NAFLD-fibrosis score. FibroSure has a high accuracy for predicting the presence of fibrosis, and reducing the need for biopsy. The European Liver Fibrosis (ELF) panel incorporates only direct markers of fibrosis such as hyaluronic acid, procollagen III amino terminal peptide, and TIMP-1, and can also be used for assessing fibrosis [27, 28]. The other less sensitive tests noted above could be useful if FibroSure and FibroScan are not available locally [28].

A noninvasive imaging method called vibration-controlled transient elastography (FibroScan) is currently being used to evaluate liver stiffness. Studies are evaluating combinations of serum biomarkers and imaging to increase diagnostic accuracy so ideally FibroScan should be used in conjunction with a serologic marker. Other imaging modalities include acoustic radiation force impulse, supersonic shear imaging, magnetic resonance elastography, and magnetic resonance imaging.

A liver biopsy should be performed if there is a discrepancy between the two testing modalities. For patients with clear evidence of cirrhosis on imaging and biochemical tests, fibrosis staging is not indicated.

It is crucial to identify risk factors in patients with chronic hepatitis C which can lead to progression of hepatic fibrosis. Factors include male sex, duration of the infection, and infection at older age. Concomitant hepatic insults like alcoholism, nonalcoholic fatty liver disease, coinfection with HIV, or chronic hepatitis B are known factors in faster progression of fibrosis in patients with chronic hepatitis C. Solid-organ transplant and immunosuppression status can also yield to rapid hepatic fibrosis progression and treatment of chronic hepatitis C is recommended [29].

4.8 Chronic Hepatitis C Therapy in Treatment-Naive Genotype 1

Genotype 1 is the most common genotype in the world, and the most difficult genotype to treat with genotype 1a having higher failure rate than genotype 1b. This is believed to be due to the incidence of baseline NS5A resistance-associated substitutions (RASs), which can be found in up to 15% of patients prior to treatment [30]. NS5A RASs negatively impact treatment outcomes by decreasing efficacy of some NS5A inhibitor-containing regimens. It is highly recommended to test for RASs in patients with genotype 1a before starting certain DAA regimens to choose the best regimen to maximize achieving SVR [7].

Four highly potent DAA oral combination regimens are recommended for patients with genotype 1 infection, although there are differences in the recommended regimens based on the HCV subtype, presence or absence of baseline NS5A resistance-associated substitutions (RASs), and presence or absence of compensated cirrhosis.

4.9 Treatment of Genotype 1a with or Without Cirrhosis

4.9.1 Elbasvir/Grazoprevir

This is a combination of NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir). It comes in a fixed daily-dose tablet containing 50 mg of elbasvir and 100 mg of grazoprevir. The 2016 AASLD/IDSA guidelines list 12 weeks of

elbasvir/grazoprevir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT 1a with or without cirrhosis [7]. In patients who demonstrate a baseline high-fold change NS5A RAS, treatment duration should be extended to 16 weeks and weight-based ribavirin should be added (AASLD/IDSA Class IIa, Level B recommendation) (Tables 4.1 and 4.2).

Recommendations for patients without cirrhosis are based on data generated in the phase 3 C-EDGE trial, and phase 2 C-WORTHY trial [31–33]. The C-EDGE trial was a randomized, placebo-controlled, parallel-group phase 3 trial that used a

Table 4.1 Initial regimens for genotype 1a treatment naive of chronic hepatitis C with no cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1a	Glecaprevir 300 mg/pibrentasvir 120 mg	8 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	8 weeks	Daily fixed	IB
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg/ dasabuvir 250 mg and weight-based ribavirin	12 weeks	Daily fixed except for dasabuvir twice daily	IA
	Simeprevir 150 mg/sofosbuvir 400 mg	12 weeks	Daily	IA
	Daclatasvir 60 mg/sofosbuvir 400 mg	12 weeks	Daily	IB
	Elbasvir 50 mg/grazoprevir 100 mg (positive baseline RASs)	16 weeks	Daily fixed	IIA,B

Table 4.2 Initial regimens for genotype 1a treatment naive of chronic hepatitis C with cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1a	Glecaprevir 300 mg/pibrentasvir 120 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Elbasvir 50 mg/grazoprevir 100 mg (positive baseline RASs)	16 weeks	Daily fixed	IIA, B

fixed-dose combination of elbasvir-grazoprevir for 12 weeks in treatment-naive patients with GT1, -4, or -6 chronic HCV in 60 centers around the world. Out of the 421 patients enrolled 382 patients were identified as monoinfected chronically with GT1, 50% (211) had GT1a and 41% (171) GT1b [31]. The data by Zeuzem et al. shows the SVR12 to be 92% (144/157) for the genotype 1a cohort that was assigned to the immediate arm of the study. Twelve percent of genotype 1a patients were identified with baseline NS5A RASs, and only 58% of these patients achieved SVR12 compared to 99% without the NS5A RAS [31]. Data from the C-EDGE TE open-label trial suggests extending the course of treatment with elbasvir/grazoprevir to 16 weeks with ribavirin in patients with baseline NS5A RASs, as they saw no virologic failures in the treatment-experienced patients [32]. Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy.

Recommendations for patients with compensated cirrhosis are based on C-EDGE and C-WORTHY trial [31–33]. C-WORTHY trial was a randomized, open-label, phase 2 trial examining the safety and efficacy of elbasvir plus grazoprevir with or without ribavirin for 12 or 18 weeks with cohort 1 being treatment-naive patients with cirrhosis, and cohort 2 being patients with a previous null response to PegIFN/ribavirin combo. A 97% (28/29) SVR12 rate had been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients [33]. Findings from the phase 3 C-EDGE trial supported the earlier findings from this phase 2 study. In the C-EDGE trial 92 patients (22% with Metavir F4 disease) were seen having had a 97% SVR12 with elbasvir/grazoprevir. Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen.

No dosage adjustments are recommended in patients with renal dysfunction or mild hepatic impairment; however it should not be used in patients with moderate-to-severe hepatic impairment (decompensated cirrhosis) [31].

4.9.2 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir) and NS5A inhibitor (pibrentasvir). It was recently approved by FDA as a pan-genotypic DAA for patients with chronic hepatitis C. It comes in a fixed daily dose with three tablets of glecaprevir 100 mg and pibrentasvir 40 mg. The 2016 AASLD/IDSA guidelines list 8 weeks of glecaprevir/pibrentasvir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT1a without cirrhosis, and 12 weeks with compensated cirrhosis [7] (Tables 4.1 and 4.2).

Recommendations for patients without cirrhosis are derived from phase II SURVEYOR 1 and ENDURANCE-1 trial [34, 35]. SURVEYOR-1 is an ongoing phase 2, two-part study designed to evaluate the safety and efficacy of this combination pill with or without RBV, for 8–12 weeks, in cirrhotic and non-cirrhotic adult

GT1 patients. Data for the non-cirrhotic group showed 97% (33/34) SVR12, and SVR12 was achieved in 98% (49/50) of treatment-naive patients [34, 35]. The ENDURANCE-1 trial is a randomized, open-labeled, phase 3 trial that evaluated the safety and efficacy of this fixed-dose combination for 8 versus 12 weeks in treatment-naive or treatment-experienced adults with GT1 chronic HCV infection without cirrhosis. SVR12 was achieved at 99.1% in 8-week arm and 99.7% in 12-week arm and it was concluded that 8 weeks of therapy was none inferior to 12 weeks [36].

Recommendations for patients with compensated cirrhosis are based on EXPEDITION-1 and EXPEDITION-2. EXPEDITION-1 is an open-label phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination for 12 weeks in treatment-naive and treatment-experienced adults with GT1, -2, -4, -5, or chronic HCV infection and compensated cirrhosis. Out of the total 146 patients enrolled 48 patients were identified to have been infected with GT1a and SVR12 was noted to be 98% (47/48), with one patient experiencing viral relapse [37]. EXPEDITION-2 looks at HIV/HCV-coinfected adults with GT1, -2, -3, -4, -5, or -6 using the glecaprevir/pibrentasvir for 8 weeks in noncirrhotic patients and 12 weeks in cirrhotic patients [38].

No dosage adjustments are recommended in patients with renal dysfunction or mild hepatic impairment; however it should not be used in patients with moderate-to-severe hepatic impairment (Child-Pugh B and C).

Most common side effects included headache (12%) and fatigue (11%).

4.9.3 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir). It comes in a daily fixed-dose pill containing sofosbuvir (400 mg) and velpatasvir (100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT1a patients with or without cirrhosis [7] (Tables 4.1 and 4.2).

Recommendations for this fixed-dose combination are based on the ASTRAL-1 trial and POLARIS-2 [39, 40]. ASTRAL-1 is a randomized, placebo-controlled, phase 3 trial using fixed-dose combination of sofosbuvir-velpatasvir for 12 weeks in treatment-naive and treatment-experienced patients with GT1, -2, -4, -5, or -6 chronic HCV. Total number of patients enrolled were 624 with 210 (34%) being identified as GT1a. In this group SVR12 was achieved in 98% (206/210) with virologic failure being very rare. One patient out of the GT1a group who failed the regimen was detected to have RAVs. This study also compared treatment results by cirrhosis and results showed that SVR12 was achieved 99% of the time in both noncirrhotics (496/501) and cirrhotics (120/121) [39].

POLARIS-2 is a phase 3 trial comparing efficacy of a fixed-dose combination of sofosbuvir-velpatasvir-voxilaprevir (SOF-VEL-VOX) for 8 weeks versus sofosbuvir-velpatasvir (SOF-VEL) for 12 weeks in treatment-naive patient with GT1–6 chronic HCV infection. Study had 941 patients enrolled, of which 465 were identified as

GT1, and 341 as GT1a. The SOF-VEL-VOX × 8 weeks cohort achieved a 95% (477/501) SVR12 and the SOF-VEL × 12 weeks cohort achieved a 98% (432/440) SVR12. When looking at data on the GT1a group treated with SOF-VEL-VOX × 8 weeks 92% (155/169) achieved SVR12 whereas 99% (170/172) of the SOF-VEL × 12 weeks achieved SVR12 [40]. There were 14 relapses observed in the SOF-VEL-VOX × 8 weeks group compared to 1 relapse in the SOF-VEL × 12 weeks group. The two combinations were also compared in cirrhotics versus noncirrhotics and the following results were obtained. In the SOF-VEL-VOX × 8 weeks cohort 96% (394/411) SVR12 was achieved in the noncirrhotic cohort, whereas 91% (82/90) SVR12 was achieved in the cirrhotic cohort. There were also observed to be 14 and 7 relapses, respectively. In the SOF-VEL × 12 weeks 98% (349/356) of SVR12 was achieved in the noncirrhotic cohort and 99% (83/84) in the cirrhotic cohort. The observed relapses in this group were 2 and 1, respectively [40].

In patients who are genotype 1a with or without cirrhosis, 12 weeks of sofosbuvir/velpatasvir should suffice to achieve SVR 12.

This combination has very tolerable side effect profile, with mild gastrointestinal adverse events associated with regimens including voxilaprevir. Most common side effects included headache, fatigue, diarrhea, and nausea.

4.9.4 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of ledipasvir/sofosbuvir treatment as a Class 1, Level A recommendation for treatment-naive GT1a patients with or without cirrhosis. These guidelines also list 8 weeks of ledipasvir/sofosbuvir treatment as a Class 1, Level B recommendation for noncirrhotic, HIV-uninfected, non-African-American whose baseline HCV RNA is less than <6 million IU/ml [7] (Tables 4.1 and 4.2).

Treatment regimen has been approved by the FDA based on two major trials, ION-1 and ION-3 [41, 42]. ION-1 open-label, randomized phase 3 trial used fixed-dose combination of ledipasvir-sofosbuvir (LDV-SOF) ± ribavirin (RBV) for 12 or 24 weeks in treatment-naive patients with GT1 chronic HCV infection. In this study by Afdhal et al., 865 patients were recruited, of which 67% (581/865) were identified as having GT1a and 16% (136/865) had cirrhosis. Data on the treatment duration and regimen choice shows that LDV-SOF ± RBV for 12 or 24 weeks achieved SVR12 of 97–99% in all arms of the trial with no notable difference in sustained virologic response in regard of genotype 1, length of the treatment, or ribavirin use. Data for treatment duration and liver disease status also showed no difference between both groups who achieved SVR12 97% in cirrhotics versus 98% in noncirrhotics [41].

ION-3 is an open-label, randomized, phase 3 trial comparing ledipasvir-sofosbuvir (LDV-SOF) with or without ribavirin (RBV) for 8 weeks and ledipasvir-sofosbuvir (LDV-SOF) for 12 weeks in treatment-naive, noncirrhotic patients

with GTI HCV. The purpose of this study was to investigate reducing the course of treatment from 12 to 8 weeks with exclusion of cirrhotic population. They recruited 647 treatment-naive patients and randomized them to three treatment groups. Treatment group one consisted of 215 patients and received LDV-SOF for 8 weeks, treatment group two consisted of 216 patients and received LDV-SOF + RBV for 8 weeks, and treatment group three consisted of 216 patients receiving LDV-SOF for 12 weeks. Kowdley et al. reported data that showed SVR12 ranging between 93 and 95% throughout all treatment arms [42]. Based on these findings no additional benefit was achieved by adding ribavirin or extending the duration of treatment. Higher level of relapse was noted in patients with high baseline HCV RNA ≥6 million. In regard to resistance data, 116 (18%) of 647 patients had baseline NS5A resistance. SVR12 was noted to be 90% (104/116) in this patient population [42].

4.10 Alternative Regimens for Genotype 1a with or Without Cirrhosis

4.10.1 Simeprevir/Sofosbuvir

This is a combination of NS3/4A protease inhibitor (simeprevir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing simeprevir (150 mg) plus sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of simeprevir/sofosbuvir as an alternative treatment with a Class 1, Level A recommendation and can be used in patients without cirrhosis [7] (Tables 4.1 and 4.2).

OPTIMIST- I trial is a randomized phase 3 open-label trial evaluating the safety and efficacy of sofosbuvir plus simeprevir for 8 or 12 weeks in treatment-naive or treatment-experienced HCV GT1 patients without cirrhosis [43]. Three hundred and ten patients were randomized into 8- or 12-week groups. We will focus on the data for the treatment-naive patients which account for 218 of the 310 (70%) patients. SVR12 was achieved in 97% of the patients with 12 weeks of treatment, whereas 85% achieved SVR12 in the 8-week arm. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance substitution [43].

4.10.2 Daclatasvir/Sofosbuvir

This is a combination of NS5A inhibitor (daclatasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing daclatasvir (60 mg) plus sofosbuvir (400 mg). The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class 1, Level B recommendation and can be used in patients without cirrhosis [7] (Tables 4.1 and 4.2).

The recommendations are based on ALLY-2 phase 3 trial which assessed the efficacy and safety of daclatasvir (DCV) and sofosbuvir (SOF) for 12 weeks in treatment-naive or -experienced patients coinfected with HIV and HCV (genotypes 1, 2, 3, or 4) [44]. Total number of patients enrolled in the study was 395, of which 106 (27%) were identified as having GT1a, and being treatment naive. We will discuss the results for the treatment-naive GT1a patients here. SVR12 was achieved in 96% (68/71) of the patients with DCV + SOF × 12-week arm, compared to 80% (28/35) in the DCV + SOF × 8-week arm. Next, we will compare the date for all GT1 patients with or without cirrhosis. For noncirrhotics SVR12 was achieved in 97% of the patients in the DCV + SOF × 12-week arm compared to 78% in the DCV + SOF × 8-week arm. For the cirrhotic patients SVR12 was achieved in 89% in the DCV + SOF × 12-week arm in contrast to 50% in the DCV + SOF × 8-week arm [44].

4.10.3 Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir and Ribavirin

This is a fixed daily-dose combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus a twice-daily dose of dasabuvir (25 mg) with weight-based ribavirin which was approved for treatment of treatment-naive GT1a chronic HCV infection without cirrhosis. Per the 2016 AASLD/IDSA guidelines this is listed as an alternative 12-week regimen with a Class 1, Level A rating [7] (Tables 4.1 and 4.2).

The recommendations are based on three major clinical trials for all GT1a patients without cirrhosis, including the SAPPHIRE-I trial, PEARL-IV trial, and TURQUOISE-II [45–47].

SAPPHIRE-I trial is a randomized, phase 3, double-blind, placebo-controlled trial evaluating the safety and efficacy of combination for 12 weeks in treatment-naive patients with chronic HCV GT1 infection. In the GT1a subgroup 95.3% (307/322) of the patients achieved SVR12 using the multitargeted regimen for 12 weeks [45].

PEARL-IV trial is a randomized, phase 3, open-label trial evaluating the safety and efficacy of ombitasvir-paritaprevir-ritonavir+dasabuvir (3D) ± ribavirin (RBV) for 12 weeks in treatment-naive patients with chronic HCV GT1a infection. SVR12 was noted to be higher in the 3D + RBV arm, 97% (97/100) compared to 90% (185/205) in the 3D arm, which elucidated to the need for ribavirin with this regimen to ensure higher SVR rates in GT1a infection [46].

TURQUOISE-II trial is a randomized, phase 3, open-label trial evaluating the safety and efficacy of 3D + RBV for 12 or 24 weeks in treatment-naive and -experienced patients with chronic HCV GT1 and compensated cirrhosis. A total of 380 patients were enrolled and 261 were identified to have GT1a infection. In the 3D + RBV × 12 weeks' arm SVR12 was achieved in 89% (124/140) of the patients and in the 3D + RBV × 24 weeks' arm SVR12 was achieved in 94% (114/121) of the patients, but this included data for treatment-naive and -experienced patients.

When looking at the data for patients with no prior treatment there were a total of 120 patients out of the 261 with GT1a infection and SVR12 was achieved in roughly 92–93% in both arms [47].

Common side effects include headache, fatigue, pruritus, nausea, insomnia, and diarrhea.

4.11 Treatment of Genotype 1b with or Without Cirrhosis

4.11.1 Elbasvir/Grazoprevir

This is a combination of NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir). It comes in a fixed daily-dose tablet containing 50 mg of elbasvir and 100 mg of grazoprevir. The 2016 AASLD/IDSA guidelines list 12 weeks of elbasvir/grazoprevir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT1b with or without cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations for patients without cirrhosis are based on data from the phase 3 C-EDGE trial and phase 2 C-WORTHY trial [31–33]. Phase 3 C-EDGE trial assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults with genotypes 1, 4, and 6. Out of the 421 total patients enrolled 171 were identified as chronically infected with GT1b. SVR12 was achieved in 99% (129/131) of the patients assigned to the immediate arm. 14% of genotype 1b patients were identified with baseline NS5A RAVs, and 94% of these patients achieved SVR12 compared to 100% without the NS5A RAVs [31]. In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear

Table 4.3 Initial regimens for genotype 1b treatment naive of chronic hepatitis C with no cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1b	Glecaprevir 300 mg/pibrentasvir 120 mg	8 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	8 weeks	Daily fixed	IB
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Simeprevir 150 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg/ dasabuvir 250 mg and weight-based ribavirin	12 weeks	Daily fixed except for dasabuvir twice daily	IA

Table 4.4 Initial regimens for genotype 1b treatment naive of chronic hepatitis C with cirrhosis [7, 26]

Genotype	Treatment	Duration	Dose	Rating of recommendation
1b	Glecaprevir 300 mg/pibrentasvir 120 mg	12 weeks	Daily fixed	IA
	Ledipasvir 90 mg/sofosbuvir 400 mg	12 weeks	Daily fixed	IA
	Elbasvir 50 mg/grazoprevir 100 mg	12 weeks	Daily fixed	IA
	Sofosbuvir 400 mg/velpatasvir 100 mg	12 weeks	Daily fixed	IA
	Paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg/ dasabuvir 250 mg and weight-based ribavirin	12 weeks	Daily fixed except for dasabuvir twice daily	IA

to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs [31].

Recommendations for patients with compensated cirrhosis are based on C-EDGE and C-WORTHY trial [31–33]. C-WORTHY trial was a randomized, open-label, phase 2 trial examining the safety and efficacy of elbasvir plus grazoprevir with or without ribavirin for 12 or 18 weeks with cohort 1 being treatment-naive patients with cirrhosis, and cohort 2 being patients with a previous null response to PegINF/ribavirin combo. A 97% (28/29) SVR12 rate had been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients [33]. Findings from the phase 3 C-EDGE trial supported the earlier findings from this phase 2 study. In the C-EDGE trial 92 patients (22% with Metavir F4 disease) were seen having had a 97% SVR12 with elbasvir/grazoprevir. Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen [31].

4.11.2 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir) and NS5A inhibitor (pibrentasvir). It was recently approved by FDA as a pan-genotypic DAA for patients with chronic hepatitis C. It comes in a fixed daily dose with three tablets of glecaprevir 100 mg and pibrentasvir 40 mg. The 2016 AASLD/IDSA guidelines list 8 weeks of glecaprevir/pibrentasvir treatment as a Class 1, Level A recommendation for treatment-naive patients with GT1b without cirrhosis, and 12 weeks with compensated cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations for patients without cirrhosis are derived from phase 2 SURVEYOR 1 and ENDURANCE-1 trials [34, 35]. SURVEYOR-1 data for the non-cirrhotic group showed 97% (33/34) SVR12 [34].

The ENDURANCE-1 trial is a randomized, open-labeled, phase 3 trial that evaluated the safety and efficacy of this fixed-dose combination for 8 versus 12 weeks in treatment-naive or treatment-experienced adults with GT1 chronic HCV infection without cirrhosis. SVR12 was achieved at 99.1% in 8-week arm and 99.7% in 12-week arm and it was concluded that 8 weeks of therapy was none inferior to 12 weeks [34].

In the SURVEYOR 1 trial 50 out of the 79 patients enrolled were treatment naive, and a SVR12 of 98% (49/50) was achieved [35].

Recommendations for patients with compensated cirrhosis are based on EXPEDITION-1 and EXPEDITION-2 [37, 38]. EXPEDITION-1 is an open-label phase 3 trial to evaluate the safety and efficacy of the fixed-dose combination for 12 weeks in treatment-naive and treatment-experienced adults with GT1, -2, -4, -5, or chronic HCV infection and compensated cirrhosis. Out of the total 146 patients enrolled 39 patients were identified to have been infected with GT1b and SVR12 was noted to be 100% (39/39) [37]. EXPEDITION-2 looks at HIV/HCV-coinfected adults with GT1, -2, -3, -4, -5, or -6 using the glecaprevir/pibrentasvir for 8 weeks in noncirrhotic patients and 12 weeks in cirrhotic patients [38]. There was (5/16) cirrhotic patients were enrolled with chronic HCV GT1b treated in the 12-week arm. In this arm (14/15) patients had achieved SVR12 (98%) with one breakthrough and 1 patient who discontinued therapy [38].

4.11.3 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir). It comes in a daily fixed-dose pill containing sofosbuvir (400 mg) and velpatasvir (100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT1b patients with or without cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations for this fixed-dose combination are based on the ASTRAL-1 trial and POLARIS-2. ASTRAL-1 trial enrolled 624 participants with 118 (19%) being identified as GT1b. In this group SVR12 was achieved in 99% (117/118) with virologic failure being very rare. There was no difference noted in the rate of SVR12 achieved in cirrhotic versus noncirrhotic patients [39].

POLARIS-2 study had 941 patients enrolled, of which 122 were identified as GT1b. SVR12 for both treatment arms SOF-VEL-VOX × 8 weeks and SOF-VEL × 12 weeks was 97%, with a single relapse observed [40].

4.11.4 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of ledipasvir/sofosbuvir treatment as a Class 1, Level A recommendation for treatment-naive GT1b patients with or without cirrhosis [7] (Tables 4.3 and 4.4).

Treatment regimen has been approved by the FDA based on two major trials, ION-1 and ION-3 [41, 42]. ION-1 enrolled 865 patients, of which 32% (273/865) were identified as having GT1b and 16% (136/865) had cirrhosis. Data on the treatment duration and regimen choice shows that LDV-SOF ± RBV for 12 or 24 weeks achieved SVR12 of 97–99% in all arms of the trial with no notable difference in sustained virologic response in regard to genotype 1, length of the treatment, or ribavirin use [41]. Data for treatment duration and liver disease status also showed no difference between both groups who achieved SVR12 97% in cirrhotics versus 98% in noncirrhotics [41].

In ION-3 trial, they recruited 647 treatment-naive patients and randomized them to three treatment groups. Treatment group one consisted of 215 patients and received LDV-SOF for 8 weeks, treatment group two consisted of 216 patients and received LDV-SOF + RBV for 8 weeks, and treatment group three consisted of 216 patients receiving LDV-SOF for 12 weeks. Kowdley et al. reported data that showed SVR12 97.7% (42/43) among patients with GT1b who were treated for 8 weeks versus 95.5% SVR 12 among patients who were treated with LDV/DOF + RBV for 8 weeks [42]. Based on these findings no additional benefit was achieved by adding ribavirin or extending the duration of treatment. Higher level of relapse was noted in patients with high baseline HCV RNA ≥6 million. In regard to resistance data, 116 (18%) of 647 patients had baseline NS5A resistance. SVR12 was noted to be 90% (104/116) in this patient population [42].

4.12 Alternative Regimens for Genotype 1b with or Without Cirrhosis

4.12.1 Simeprevir/Sofosbuvir

This is a combination of NS3/4A protease inhibitor (simeprevir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing simeprevir (150 mg) plus sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of simeprevir/sofosbuvir as an alternative treatment with a Class 1, Level A recommendation and can be used in patients without cirrhosis [7] (Tables 4.3 and 4.4).

Recommendations are based on OPTIMIST-I which enrolled 310 patients which were randomized into 8- or 12-week groups. Focusing on the data for the treatment-naive patients, which accounted for 218 of the 310 (70%) patients, showed that SVR12 was achieved in 97% of the patients with 12 weeks of treatment versus 85% in the 8-week arm. There was also no difference in SVR12 based on genotype 1 subtype or presence of the baseline Q80K resistance substitution [43].

4.12.2 Daclatasvir/Sofosbuvir

This is a combination of NS5A inhibitor (daclatasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily pill containing daclatasvir (60 mg) plus sofosbuvir (400 mg). The dose of daclatasvir may need to increase or decrease when used

concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class 1, Level B recommendation and can be used in patients without cirrhosis [7] (Tables 4.3 and 4.4).

The recommendations are based on ALLY-2 phase 3 trial which had 395 patients enrolled, of which 18 (5%) were identified as having GT1b, and being treatment naive. We will discuss the results for the treatment-naive GT1b patients here. SVR12 was achieved in 100% (12/12) of the patients in the 12-week arm, compared to 50% (3/6) in the 8-week arm. For noncirrhotics SVR12 was achieved in 97% (70/72) of the patients in the 12-week arm compared to 78% (28/36) in the 8-week arm. For the cirrhotic patients SVR12 was achieved in 89% (8/9) in the 12-week arm in contrast to 50% (2/4) in the 8-week arm for treatment-naive patients [44].

4.12.3 Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

This is a fixed daily-dose combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus a twice-daily dose of dasabuvir (25 mg) with weight-based ribavirin which was approved for treatment of treatment-naive GT1b chronic HCV infection with or without cirrhosis. Per the 2016 AASLD/IDSA guidelines this is listed as an alternative 12-week regimen with a Class 1, Level A rating [7] (Tables 4.3 and 4.4).

The recommendations are based on three major clinical trials for all GT1a patients without cirrhosis, including the SAPPHIRE-I trial, PEARL-IV trial, and TURQUOISE-II [45–47].

SAPPHIRE-I trial showed that in GT1b subgroup 98% (148/151) of the patients achieved SVR12 using the multitargeted regimen for 12 weeks [45].

In the PEARL-IV trial SVR12 for GT1b infection was noted to be similar in the 3D + RBV arm 99.5% (209/210) and 99% (207/209) in the 3D arm. Rates of virologic failure were higher without ribavirin than with ribavirin among patients with genotype 1a infection but not among those with genotype 1b infection [46].

In the TURQUOISE-II trial a total of 380 patients were enrolled and 119 were identified to have GT1b infection. In both the 12-week and 24-week arms SVR was similar (99% and 100%, respectively) in patients with GT1b infection [47].

4.13 Treatment of Genotype 2 with or Without Cirrhosis

4.13.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the 2016 AASLD/IDSA guidelines this is listed as an 8-week regimen for patients without cirrhosis with a Class 1, Level A rating. For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level B rating [7] (Tables 4.5 and 4.6).

Table 4.5 Initial regimens for genotypes 2, 3, 4, 5, and 6 treatment naive of chronic hepatitis C with no cirrhosis [7, 26]

Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Glecaprevir 300 mg/ pibrentasvir 120 mg, daily dose for 8 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily dose for 8 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily for 8 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily for 8 weeks
Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks
Daclatasvir 60 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Daclatasvir 60 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks
		Elbasvir 50 mg/ grazoprevir 100 mg, daily dose for 12 weeks	
		Paritaprevir 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg and weight-based ribavirin for 12 weeks	

Table 4.6 Initial regimens for genotypes 2, 3, 4, 5, and 6 treatment naive of chronic hepatitis C with cirrhosis [7, 26]

Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Glecaprevir 300 mg/ pibrentasvir 120 mg, daily dose for 12 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily dose for 12 weeks	Glecaprevir 300 mg/ pibrentasvir 120 mg daily for 8 weeks	Glecaprevir 300 mg/pibrentasvir 120 mg daily for 12 weeks
Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg, daily dose for 12 weeks
Daclatasvir 60 mg/ sofosbuvir 400 mg, daily dose for 16–24 weeks	Sofosbuvir 400 mg/ velpatasvir 100 mg/ voxilaprevir 100 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks	Ledipasvir 90 mg/ sofosbuvir 400 mg, daily dose for 12 weeks
	Daclatasvir 60 mg/ sofosbuvir 400 mg with weight-based ribavirin daily for 24 weeks	Elbasvir 50 mg/ grazoprevir 100 mg, daily dose for 12 weeks	
		Paritaprevir 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg and weight-based ribavirin for 12 weeks	

Kowdley et al. presented their data from ENDURANCE-2 trial at AASLD 2016 about the use of glecaprevir/pibrentasvir [48]. They had 302 patients recruited for the study cohort infected with genotype 2 and 202 of them were randomized for placebo-controlled groups. There was 70% of the cohort population treatment naive with no cirrhosis. They were all treated with glecaprevir 300 mg/pibrentasvir 120 mg daily for 12 weeks and the SVR 12 rate was achieved in 99% of the cohort. It is worth to mention that one patient of the study achieved SVR 4 who was lost for follow-up [48].

Glecaprevir/pibrentasvir was actually investigated for shorter course of therapy at 8 weeks. In phase 2, single-arm study, Hassanein et al. examined in SURVEYOR-2 trial 203 patients with no cirrhosis infected with genotypes 2, 4, 5, and 6. There were 142 (70%) patients with genotype 2 and 137 (96%) of them were treatment naive. All of them received 8 weeks of daily fixed dose of glecaprevir 300 mg/pibrentasvir 120 mg and the SVR rate was 99% achieved in 135/137 of treatment-naive patients [49].

From both trials mentioned above, it was elucidated that both regimens are clearly highly effective in the treatment of chronic hepatitis C in patients infected with genotype 2 without cirrhosis using 8 or 12 weeks' regimens [48, 49].

In compensated cirrhosis, EXPEDITION-1, a phase 3 open-label single-arm trial, had investigated glecaprevir/pibrentasvir in 146 patients with compensated cirrhosis infected with genotypes 1, 2, 4, 5, and 6. All of the patients had received 12 weeks of daily fixed dose of glecaprevir 300 mg/pibrentasvir 120 mg and SVR 12 was achieved in 99% of participants from all genotypes [37]. On the other hand, in EXPEDITION-2, the cohort was smaller where they enrolled 31 patients infected with a genotype 2; between naive and experienced all 31 patients achieved SVR 12 successfully [38].

Recommendations for patients without cirrhosis are derived from phase 2 SURVEYOR 1 and ENDURANCE-2 trial. SURVEYOR-1 data for the noncirrhotic group showed 97% (33/34) SVR12.

ENDURANCE-2 trial is a randomized, double-blinded, phase 3 trial to evaluate the safety and efficacy of this fixed-dose regimen for 12 weeks in treatment-naïve or treatment-experienced adults with GT2 chronic HCV infection without cirrhosis. Out of the 202 patients enrolled into the treatment arm 141 (70%) were treatment naive. Overall SVR12 was noted to be 99% in this group.

4.13.2 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir) and NS5A inhibitor (velpatasvir). It comes in a daily fixed-dose pill containing sofosbuvir (400 mg) and velpatasvir (100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT2 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

Recommendations for this fixed-dose combination are based on the ASTRAL-1, ASTRAL-2, and POLARIS-2 trials. ASTRAL-1 trial enrolled 624 participants with 104 (17%) being identified as GT2. In this group SVR12 was achieved in 100% of the patients. There was no difference noted in the rate of SVR12 achieved in cirrhotic versus noncirrhotic patients [39].

ASTRAL-2 trail is a randomized, placebo-controlled, phase 3 trial using a fixed-dose combination of sofosbuvir-velpatasvir (SOF-VEL) for 12 weeks compared with sofosbuvir plus ribavirin (SOF + RBV) in treatment-naive and treatment-experienced patients with GT2 chronic HCV. A total of 266 patients were randomized into either SOF-VEL arm or SOF + RBV arm. There were roughly 14% cirrhotics and treatment-experienced patients in both arms. SVR 12 rates were found to be higher in SOF-VEL compared to SOF + RBV, 99% vs. 94%, respectively [50]. Patients with cirrhosis were all successfully able to achieve SVR12 with 12 weeks of sofosbuvir/velpatasvir. Similar findings were seen in patients with prior virologic failure. The treatment was well tolerated and there was not any reported case of anemia [50].

POLARIS-2 study had 941 patients enrolled, of which 116 were identified as infected with GT2. SVR12 for SOF-VEL-VOX × 8 weeks was 97% (61/63) and SOF-VEL × 12 (53/53) weeks was 100% [41].

4.14 Alternative Regimens for Genotype 2 with or Without Cirrhosis

4.14.1 Daclatasvir/Sofosbuvir

Daclatasvir NS5A inhibitor (60 mg) and sofosbuvir (400 mg) was not approved for treatment of genotype 2 infection, but since daclatasvir maintains adequate activity against genotype 2 and in association with sofosbuvir has shown high SVR rates in treatment-naive patients it has been recommended as an alternative regimen. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class IIa, Level B rating in patients without cirrhosis, and in compensated cirrhosis they recommend therapy duration to range from 16 to 24 weeks with Class IIa, Level B rating [7] (Tables 4.5 and 4.6).

In ALLY-2 trial, Wyles et al. had treated 13 patients with no cirrhosis; 2 of them were treatment experienced, with daily combination of daclatasvir 60 mg/sofosbuvir 400 mg for 12 weeks. SVR 12 was achieved in 100% of the group [44]. Sulkowski et al. also published good evidence of 24 weeks of daclatasvir/sofosbuvir used for genotype 2 with SVR12 rate at 92% of 26 patients enrolled in this trial. For patients who develop intolerance to prior recommended regimens, daclatasvir/sofosbuvir can be used for 12 or 24 weeks depending on disease staging and prior virologic failure [51].

4.15 Treatment of Genotype 3 with or Without Cirrhosis

4.15.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the 2016 AASLD/IDSA guidelines this is listed as an 8-week regimen for patients without cirrhosis with a Class 1, Level A rating. For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level A rating [7] (Tables 4.5 and 4.6).

In ENDURANCE-3 trial, Foster et al. had compared the efficacy of glecaprevir/pibrentasvir in patients with genotype 3 at 8 and 12 weeks. The study recruited 348 patients infected with genotype 3 treatment naive without cirrhosis and randomized first into two groups, glecaprevir 300 mg/pibrentasvir 120 mg (233) versus sofosbuvir 400 mg/daclatasvir 60 mg (115). Later on it was decided to add another arm of the study to investigate the efficacy of glecaprevir/pibrentasvir for 8 weeks (157) [52]. SVR12 rate was reached successfully at 95% of the both arms (222/233, 149/157). SVR12 rate in 8 weeks arm was found none inferior to 12 weeks' arm of glecaprevir/pibrentasvir. Both of these arms were eventually found non-inferior to the other arm of sofosbuvir and daclatasvir which considered the standard of treatment (SVR12 rate 97%). Virologic failure of 8 weeks' arm was noted in six subjects (one virologic breakthrough and five relapses), meanwhile four virologic failures were recorded among 12 weeks' arm (one virologic breakthrough and three relapses) [52].

In SURVEYOR II phase 2 trial, 48 patients with compensated cirrhosis treatment naive infected with genotype 3 were randomized into 2 groups with 24 patients each. First group received 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg versus 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg with weight-based ribavirin [49]. All patients in both arms achieved SVR12 and baseline RAVs appeared to have no impact on SVR12. It was concluded for those GT3 treatment-naive patients with compensated cirrhosis that treatment with 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg suffices to achieve SVR12 regardless of the use of ribavirin [49].

4.15.2 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir 400 mg) and NS5A inhibitor (velpatasvir 100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT3 patients with or without cirrhosis [5]. RAS testing for Y93H is recommended for cirrhotic patients and if present it is recommended that ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered [7] (Tables 4.5 and 4.6).

Foster et al. in ASTRAL 3 trial screened 652 patients infected with genotype 3 [50]. Out of those, 558 patients were randomized into 2 groups and 552 patients received treatment. 277 patients received 12 weeks of daily fixed dose of sofosbuvir 400 mg/velpatasvir 100 mg while 275 patients received 24 weeks of sofosbuvir 400 mg and weight-based ribavirin (1000 mg < 75 kg and 1200 mg > 75 kg). The SVR12 rate was 95% with sofosbuvir/velpatasvir arm in comparison to 80% SVR12 among those who received sofosbuvir and ribavirin for 24 weeks. For treatment-naive patients without cirrhosis, the SVR rate was 98% (16/163) and 93% (40/43) for treatment-naive patients with compensated cirrhosis versus 73.5% (33/45) for those with compensated cirrhosis who were treated with sofosbuvir and ribavirin. It's worth mentioning that SVR12 was 88% for those who had NS5A RAVs at the baseline and 84% (21/25) was noted in subjects with detected Y93H variants at the baseline. It is recommended to add ribavirin for those patients with compensated cirrhosis who do have detectable level of the aforementioned variant [50].

In POLARIS 2 and 3, Jacobson et al. have looked into 12-week treatment with sofosbuvir/velpatasvir versus 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in patients infected with genotype 3 with or without cirrhosis [40]. In Polaris 2 phase 3 study 89 patients infected with genotype 3 were treated with sofosbuvir/velpatasvir for 12 weeks and 97% (86/89) achieved SVR12 with no virologic failure and this adds another strong evidence for this regimen's efficacy in treating genotype 3 chronic HCV in noncirrhotic population [40].

In POLARIS 3 study, the cohort included 229 patients infected with genotype 3 and compensated cirrhotics were randomized into 2 groups. 109 patients received 12 weeks of daily fixed dose of sofosbuvir 400 mg/velpatasvir 100 mg and 110 patients received 8 weeks of sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg. The SVR rate achieved was 96% in both arms of the study (105/109) and (106/110), respectively. All patients with detected Y93H at baseline had achieved SVR in the sofosbuvir/velpatasvir arm [53].

4.16 Alternative Regimens for Genotype 3 with or Without Cirrhosis

4.16.1 Daclatasvir/Sofosbuvir

Daclatasvir NS5A inhibitor (60 mg) and sofosbuvir (400 mg) is approved for the treatment of genotype 3 infection. The 2016 AASLD/IDSA guidelines list 12 weeks of daclatasvir/sofosbuvir as an alternative treatment with a Class I, Level A rating in patients without cirrhosis, and in compensated cirrhosis they recommend therapy duration of 24 weeks with or without weight-based ribavirin with Class IIa, Level B rating [7] (Tables 4.5 and 4.6).

In ALLY-3 phase 3 trial, Nelson et al. had evaluated the use of 12 weeks' regimen of daclatasvir 60 mg (DCV)/sofosbuvir 400 mg (SOF) in noncirrhotic and cirrhotic patients infected with genotype 3 [54]. There were 152 patients enrolled with 101

patients being treatment naive and 51 patients being treatment experienced; both groups received 12 weeks of the aforementioned treatment; however we will focus on the data for the treatment-naive group. 19% (19/101) of the treatment-naive patients had compensated cirrhosis. The SVR12 rate was 90% (90/101) among all treatment-naive patients; patients without cirrhosis achieved 97% (73/75) SVR12 whereas cirrhotic patients who were treated with same regimen for the same length of therapy achieved an SVR12 of 58% (11/19) only [54].

In the follow-up, ALLY 3+ trial was a phase 3 open-label randomized trial of DCV + SOF + RBV for 12 versus 16 weeks in both treatment-naive or -experienced chronic HCV GT3 with advanced fibrosis or compensated cirrhosis. SVR12 was achieved in 88% (21/24) of patients in the 12 weeks' arm, and 92% (24/26) in the 16 weeks' arm. In regard to patients with cirrhosis 83% achieved SVR12 in the 12 weeks' arm and 89% in the 16 weeks' arm [54].

The results from the ALLY-3+ study suggested that compensated cirrhotic patients with genotype 3 would benefit from treatment extension, and this hypothesis was confirmed by data from the real-world cohort DCV European compassionate-use program [56]. This analysis included 102 genotype 3 chronic hepatitis C patients considered at high risk of hepatic decompensation or death within 12 months if left untreated. Participants were treated with DCV + SOF ± RBV × 24 weeks; however providers could opt for a shorter course, or addition of ribavirin. In treatment-naive patients on DCV + SOF 92% achieved SVR12 whereas 100% achieved SVR12 with DCV + SOF + RBV. For cirrhotic patients 89% achieved SVR12 on DCV + SOF and 88% on DCV + SOF + RBV. 85% of the GT3-infected patients had cirrhosis and there were some notable variations with SVR12 rate and liver disease severity. SVR12 rates were higher among patients with Child-Pugh A cirrhosis compared to those with Child-Pugh B and C (80–100% vs. 70%) [55]. Between both arms which were treated with or without ribavirin, it was concluded that SVR12 was comparable independently from ribavirin use (95.9% vs. 81.3%). As it was mentioned earlier in ENDURANCE-3 trial, gravida 15 patients were randomized in the sofosbuvir 400 mg/daclatasvir 60 mg arm for 12 weeks. SVR rate achieved in this cohort was 97% and 95% (20/21) with baseline NS5A RASs [55].

The presence of NS5A RAS baseline was associated dramatically with reduced SVR12 rates among patients infected with genotype 3. The presence of NS5A Y93H was found to be related to decreased SVR12 in 7/13 (54%) with baseline NS5A Y93H who were treated in ALLY-3 [54]. On the other hand, in those who did not have NS5A Y93H the SVR12 was 92% (149/162). Also, cirrhosis felt to be a factor contributed to less SVR12 rate in those with baseline NS5A RASs. Another RAS detected was associated with lower SVR12 like A30K. In ALLY-3 trial, patients without cirrhosis who did have detectable level of this RAS all achieved SV2 12 (9/9). However, among those with compensated cirrhosis, 1/5 only achieved SVR12 but 2/5 were NS5A Y93H positive and it felt to be hard to differentiate the real reason for not achieving SVR12 in those patients [54].

4.16.2 Sofosbuvir/Velpatasvir/Voxilaprevir

NS5B polymerase inhibitor (sofosbuvir 400 mg), NS5A inhibitor (velpatasvir 100 mg), and NS3/4A protease inhibitor (voxilaprevir 100 mg) are new 12-week regimen approved by FDA recently to treat DAA-experienced patients with cirrhosis and Y93H [7] (Table 4.6).

In POLARIS-3 trial this combination was used to examine 8-week non-inferiority in comparison to 12 weeks of sofosbuvir and velpatasvir. It included patients infected with genotype 3 and compensated cirrhosis. 229 were randomized into 2 groups. 109 patients received 12 weeks of daily fixed dose of sofosbuvir 400 mg/velpatasvir 100 mg and 110 patients received 8 weeks of sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg. The SVR rate achieved was 96% in both arms of the study (105/109) and (106/110), respectively. All patients with detected Y93H at baseline had achieved SVR6 in 8-week SOF-VEL-VOX arm and 4 in 12-week SOF-VEL arm [53].

4.17 Treatment of Genotype 4 with or Without Cirrhosis

4.17.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the updated 2016 AASLD/IDSA guidelines this is listed as an 8-week regimen for patients without cirrhosis with a Class 1, Level A rating [7] (Tables 4.5 and 4.6).

In part 4 SURVEYOR-2 study, 22 patients with genotype 4 were treated with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg. SVR12 rate was achieved in 100% of the patients [49]. In ENDURANCE-4, Asselah et al. recruited 121 patients with genotypes 4, 5, and 6, noncirrhotic (majority F0-1), treatment naive or experienced with interferon or PegIFN with ribavirin, or sofosbuvir with ribavirin or without PegIFN. They were treated with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg with 99% (75/76) achieving SVR12 in genotype 4 [56].

In an open-label, single-arm, multicenter study (SURVEYOR-2 part 4) phase 2 trial the use of 8 weeks of glecaprevir 300 mg and pibrentasvir 120 mg was investigated. There were 46 patients (23%) infected with genotype 4 who achieved SVR12 rates of 93% (43/46), with 1 discontinuation and 2 missing SVR12 data [49].

For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level B rating [7]. In EXPEDITION-1, Forns et al. looked at using glecaprevir 300 mg/pibrentasvir 120 mg for patients with compensated cirrhosis. They enrolled 146 patients with compensated cirrhosis secondary to chronic hepatitis C; 11% of the cohort was infected with genotype 4. Their results show that 100% of the patients enrolled achieved SVR with this regimen [37].

4.17.2 Elbasvir/Grazoprevir

This is a combination of NS5A inhibitor (elbasvir) and NS3/4A protease inhibitor (grazoprevir). It comes in a fixed daily-dose tablet containing 50 mg of elbasvir and 100 mg of grazoprevir. The 2016 AASLD/IDSA guidelines list 12 weeks of elbasvir/grazoprevir treatment as a Class 2a, Level B recommendation for treatment-naive patients with GT 4 with or without cirrhosis [7] (Tables 4.5 and 4.6).

Based on data from pooled analysis from phase 2/3 trials presented by Asselah et al. at AASLD 2015, 103 patients were enrolled with 66 of them being treatment naive and 6 patients being cirrhotic. 56 patients were treated with 12 weeks of daily dose of elbasvir/grazoprevir and 10 patients were treated with elbasvir/grazoprevir and ribavirin. Results showed that 97% (64/66) achieved SVR12 including all 10 patients who received ribavirin. 6/6 treatment naive with compensated cirrhosis also achieved SVR12 [58].

4.17.3 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir 400 mg) and NS5A inhibitor (velpatasvir 100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level A recommendation for treatment-naive GT4 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

Favorable data generated from ASRTRAL-1 and POLARIS-2 trial strongly supports the use of sofosbuvir 400 mg/velpatasvir 100 mg for 12 weeks to treat genotype 4 HCV infection with or without cirrhosis [39, 40]. In ASTRA-1 trial, 116 (19%) patients infected with genotype 4 were treated with 12 weeks of sofosbuvir 400 mg/velpatasvir 100 mg; 27 of them had compensated cirrhosis. The SVR12 rate was achieved at 100% in all genotype 4 patients [39].

In POLARIS-2 trial, 57 patients with genotype 4 were treated with 12-week sofosbuvir 400 mg/velpatasvir 100 mg and showed that SVR12 rate was achieved in 98% with one recorded relapse and no virologic failure [40].

4.17.4 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of ledipasvir/sofosbuvir treatment as a Class 2a, Level B recommendation for treatment-naive GT 4 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

Kohli et al. reported in the SYNERGY trial (single-center open-label trial) promising data regarding treatment of genotype 4 patients. They recruited 21 patients infected with genotype 4; 7 of them were cirrhotic. One patient did not complete treatment and the rest all successfully achieved SVR12 (95%), with intention-to-treat analysis SVR12 rate of 100% including all patients with compensated cirrhosis

[58]. Also, data from Abergel et al. reported SVR12 95% in their cohort, 21/22 treated with 12 weeks of ledipasvir/sofosbuvir [59].

4.18 Alternative Regimens for Genotype 4 with or Without Cirrhosis

4.18.1 Paritaprevir/Ritonavir/Ombitasvir and Ribavirin

This is a fixed daily-dose combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin used for the treatment of genotype 4 HCV infection with or without compensated cirrhosis. According to AASLD/IDSA guidelines these recommendations are Class 1, Level A [7] (Tables 4.5 and 4.6).

In PEARL-I trial Hézode et al. had tested the efficacy of this combination with and without ribavirin on patients infected with genotype 4. In this multicenter, randomized, phase 2b trial, 135 noncirrhotic patients were enrolled infected with genotype 4 who were randomized to be treated with paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) with or without weight-based ribavirin. 86 patients were treatment naïve; 42 of them received paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin daily and 44 of them received paritaprevir (150 mg), ritonavir (100 mg), and ombitasvir (25 mg) without ribavirin daily. SVR12 rate was achieved in 100% among ribavirin group and 90.9% among other group which did not receive ribavirin [60].

In AGATE-II trial, Esmat et al. treated 100 noncirrhotic, treatment-naive and -experienced (with interferon-based regimen) patients infected with genotype 4 with daily combination of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg), and weight-based ribavirin which resulted in SVR12 rate of 94%.

In AGATE-1 trial, Asselah et al. evaluated the efficacy of this combination with ribavirin in the treatment of genotype 4 patients with compensated cirrhosis. 120 patients with compensated cirrhosis were randomized into two groups, 12 weeks versus 16 weeks of therapy with paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin; 51% of the patients in the 12-week arm and 48% in 16-week arm were treatment naive. The SVR12 rate was 96% in 12-week arm versus 100% in 16-week arm [61].

Based on the excellent data from trials mentioned above 12 weeks of paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg) plus weight-based ribavirin would suffice and serve a as good alternative therapy to first-line regimens for the treatment of genotype 4 with or without cirrhosis.

4.19 Treatment of Genotype 5–6 HCV Infection

4.19.1 Glecaprevir/Pibrentasvir

This is a combination of NS3/4A protease inhibitor (glecaprevir 300 mg) and NS5A inhibitor (pibrentasvir 120 mg). Per the updated 2016 AASLD/IDSA guidelines this

is listed as an 8- or 12-week regimens for patients without or with cirrhosis, respectively, with a Class 1, Level A rating [7] (Tables 4.5 and 4.6).

In ENDURANCE-4, Asselah et al. recruited 121 patients with genotype 4, 5, and 6, noncirrhotic (majority F0-1), treatment naive or experienced with interferon or PegIFN with ribavirin, or sofosbuvir with ribavirin or without PegIFN. They were treated with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg. The SVR12 rate was 100% among patients with genotypes 5 (26/26) and 6 (19/19) [56]. Kwo et al. in SURVOYER-2 study treated 12 patients with genotypes 5 and 6 with 12 weeks of glecaprevir 300 mg and pibrentasvir 120 mg and the SVR12 rate was achieved in 100% [34].

In an open-label, single-arm, multicenter study (SURVYOR-2 part 4) phase 2 trial, 8-week glecaprevir 300 mg and pibrentasvir 120 mg was investigated. There were 46 patients (23%) infected with genotype 5 treated with 8 weeks of glecaprevir 300 mg/pibrentasvir 120 mg. The SVR rate achieved was 100% (2/2) in genotype 5 and 90% (9/10) in genotype 6 with 1 patient missing SVR12 data testing; intention to treat SVR12 was 100% [50]. For patients with compensated cirrhosis it is recommended to treat for a 12 weeks' duration with a Class 1, Level A rating [7].

In EXPEDITION-1, Forns et al. looked into using glecaprevir 300 mg/pibrentasvir 120 mg for patients with compensated cirrhosis. They enrolled 146 patients with compensated cirrhosis secondary to chronic hepatitis C; 7 of them were infected with genotypes 5 and 6. They received 12 weeks of glecaprevir 300 mg/pibrentasvir 120 mg and the SVR12 rate was achieved at 100% in both genotypes [37].

4.19.2 Sofosbuvir/Velpatasvir

This is a combination of NS5B polymerase inhibitor (sofosbuvir 400 mg) and NS5A inhibitor (velpatasvir 100 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of sofosbuvir/velpatasvir treatment as a Class 1, Level B recommendation for treatment-naive GT 5–6 patients with or without cirrhosis [7] (Tables 4.5 and 4.6).

In ASTRAL-I trial, Feld et al. had investigated sofosbuvir 400 mg/velpatasvir 100 mg for 12 weeks for infected patients with genotypes 5 and 6. There were 35 patients with genotype 5 (5 of them were with compensated cirrhosis) and 41 patients with genotype 6 (6 of them were with compensated cirrhosis) who were treated with 12 weeks of sofosbuvir 400 mg/velpatasvir 100 mg. The SVR12 rate was achieved in 96% with genotype 5 and 100% among those with genotype 6. All patients with compensated cirrhosis had achieved SVR12 among both genotypes [40].

4.19.3 Ledipasvir/Sofosbuvir

This is a combination of NS5A inhibitor (ledipasvir) and NS5B polymerase inhibitor (sofosbuvir). It comes in a daily fixed-dose pill containing ledipasvir (90 mg) and sofosbuvir (400 mg). The 2016 AASLD/IDSA guidelines list 12 weeks of

Table 4.7 IFN-free treatment regimens available for treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, recommended for each HCV genotype/subtype [26][a]

	Pan-genotypic			Genotype-specific		
Genotype	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
1a	Yes	Yes	No[b]	Yes	Yes	No
1b	Yes	Yes	No[b]	Yes	Yes	Yes
2	Yes	Yes	No[b]	No	No	No
3	Yes	Yes	Yes	No	No	No
4	Yes	Yes	No[b]	Yes	Yes	No
5	Yes	Yes	No[b]	Yes	No	No
6	Yes	Yes	No[b]	No	Yes	No

DSV dasabuvir, *EBR* elbasvir, *GLE* glecaprevir, *GZR* grazoprevir, *IFN* interferon, *LDV* ledipasvir, *OBV* ombitasvir, *PIB* pibrentasvir, *PTV* paritaprevir, *r* ritonavir, *SOF* sofosbuvir, *VEL* velpatasvir, *VOX* voxilaprevir

[a]Recommendations can be specific to certain subgroups; please see the text

[b]Triple combination therapy is efficacious in these genotypes; however it is not useful due to the efficacy of double combination regimens

ledipasvir/sofosbuvir treatment as a Class 2a, Level B recommendation for treatment-naive GT5–6 patients [7] (Tables 4.5 and 4.6).

In a small study from New Zealand, Gane et al. had used ledipasvir (90 mg) and sofosbuvir (400 mg) for 12 weeks in the treatment of genotype 6-infected patients; 25 patients (2 with cirrhosis) were treated with 12 weeks of ledipasvir (90 mg) and sofosbuvir (400 mg) and 24 of them achieved SVR12 (96%). The one patient who did not achieve SVR12 withdrew treatment at week 8 after relapsing post-week 4 [62]. It was reported that ledipasvir does not have good in vitro activity against genotype 6 subtype e; otherwise it holds good in vitro activity against all other genotype 6 subtypes [62].

Abergel et al. had reported treating 41 patients with genotype 5; 39 of them had achieved SVR12 (95%). Data still limited on treating patients with genotype 5 using ledipasvir (90 mg) and sofosbuvir (400 mg) [59]. A summary of IFN-free treatment regimens available for treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis, recommended for each HCV genotype/subtype is given in Table 4.7.

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