Current Management of HCV Genotype 3 Infection

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Hepatitis C virus (HCV) genotype 3 (HCV-G3) is one of the seven recognized genotypes [1]. HCV-G3 is the second most common genotype accounting for 22% of all infections globally [2, 3]. Although three-quarters of them occur in South Asia, where it is endemic, the 3a subtype is an "epidemic subtype" widely distributed geographically, probably associated with injecting drug use [4].

HCV-G3 is significantly associated with faster progression of fibrosis [5, 6], a greater risk for hepatocellular carcinoma (HCC) [6–8], and higher mortality as compared with the other genotypes [9]. The introduction of all oral interferon free based on direct-acting antiviral (DAAs) therapies has been a watershed for the management of HCV infection. DAAs therapies have led to more than 90% sustained virological response (SVR) rates, which is equivalent to a cure. This is possible for all genotypes and for all subgroups of patients including those who have been considered difficult to treat with previous regimes. The discussion, therefore, has moved to how we eliminate HCV infection by increasing the number of treated patients. In this chapter, we discuss briefly the HCV-G3 epidemiology and special characteristics and we review new advances in HCV therapies [10–12].

7.1 Introduction

7.1.1 Epidemiology

HCV infection is a serious public health problem with rising morbidity and mortality rates [13]. It is estimated that there are 71–80 million viremic HCV patients worldwide [14, 15], but most of them are unaware of their infection. Several studies on the global, regional, and national prevalence and genotype distribution of HCV

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infection highlighted significant geographical differences [16–19]. Specifically, HCV-G3 is the second most common genotype in Europe but is more prevalent in Asia (40%) where it predominates in India (54%), Malaysia (59%), and Pakistan (79%) [3]. HCV-G3 is also predominant (>43%) in some European countries (Denmark, Finland, United Kingdom, and Norway) [18]. Furthermore, the genotype distribution is a dynamic process, partly due to migration. For instance, a recent study in Turkey reported HCV-G3 prevalence of 46%, a rate remarkably higher than that from previous Turkish findings [20].

Drug use is the main mode of HCV acquisition in Western populations and an increasing problem for HCV spread in many developing countries [21, 22]. Over the last ten years HCV-G3 was reported as the most frequent genotype among people who inject drugs (PWID) (>50%), with genotype 1 infection being the second most common. Therefore, HCV genotype 1 and HCV-G3 tend to be the most common genotypes in countries with a high rate of transmission among drug users [23, 24]. China, United States, and the Russian Federation have by far the largest HCV-positive PWID populations. PWID are now at the heart of the HCV epidemics in the developed countries [22]. More specifically, HCV subtype 3a, which originated from Asia, has spread widely among PWID and also among other patient groups in industrialized countries [25, 26]. In the United Kingdom, for example, HCV genotype 1 and HCV-G3 account for approximately 45% and 40% of HCV infections [27] and in some other European countries (including Greece, Poland, and Sweden), HCV-G3 accounts for up to 30% of HCV infections.

Data based on the EUROSIDA cohort have shown significant differences in the proportion of patients with HCV-G3 among HCV-HIV co-infected patients from 24.4% in southern Europe/Israel/Argentina and 39.8% in Eastern Europe [28]. In Poland, HCV-G3 was more frequent in the HCV-HIV co-infected population than in the overall HCV infected population (40.4% vs 13.8%) [29].

HCV-G3 was also the second most common genotype reported in monocentric studies on patients who had had liver transplants (14.3%, 10.8%, and 11.6% in Austria [30], France [31], and Poland [32], respectively).

7.1.2 Special Characteristics of HCV Genotype 3

Regarding HCV clearance, acutely HCV-infected patients are much more likely to spontaneously clear HCV if they are infected with HCV-G3 than HCV genotype 1 [33]. Moreover, chronically infected HCV-G3 patients had higher SVR rates after shorter treatment with PegIFNα/RBV therapy when compared with those with chronic genotype 1 infection [34]. One of the possible reasons could be that HCV-G3 induces greater interferon transcription than either genotype 1a or 1b [35]. On the other hand, a growing body of evidence suggests that patients infected with HCV-G3 could have a worse clinical outcome compared with other genotypes. In a study from the United States, after adjusting for demographic and clinical characteristics, the risks of cirrhosis and HCC were 31 and 80% higher, respectively, in patients with HCV-G3 compared with genotype 1 [6]. In another study, HCV-G3

patients were consistently at higher risk of liver-related events than those with genotype 1 and presented higher mortality rates. In addition, the risk of decompensated cirrhosis was 42% higher and HCC risk was 63% higher [8].

Referring to steatosis, it is so common in HCV infection that it was used as a diagnostic tool in the pre-serology era to identify patients with chronic non-A, non-B hepatitis [36–40]. The notion that HCV-G3 directly causes steatosis, rests on three lines of evidence: (1) In patients with HCV-G3, steatosis is more frequent and severe [41, 42], (2) the severity correlates with the level of HCV replication [41, 42], and (3) may decrease or disappear upon successful treatment with antivirals [41, 43, 44]. On the contrary, in most patients with non-3 genotypes, steatosis correlates with metabolic variables, such as body mass index [42], and tends to persist even in case of SVR [43, 44]. Thus, steatosis can be classified into 2 types according to HCV genotypes: metabolic steatosis, which is associated with features of metabolic syndrome and insulin resistance in patients infected with non-genotype 3 and viral steatosis, which is correlated with viral load and hypolipidemia in patients infected with HCV-G3 [45]. Interestingly, many mechanisms accounting for HCV-related steatosis can also cause insulin resistance (IR) but patients with the highest degrees of viral steatosis (e.g., infected with HCV-G3 with severe steatosis) do not necessarily present high levels of IR, and vice versa. In HCV-G3 infection, IR levels are comparable in patients with vs without steatosis [45]. Studies have shown that the homeostatic model assessment of insulin resistance (HOMA-IR) score levels are higher in patients with genotypes 1 and 4 [46], and that patients with HCV-G3 are those in whom HOMA-IR levels are the lowest [47]. These findings are not univocal: in a study from Greece, HOMA-IR levels were comparable across viral genotypes [48]; at best, these results suggest that the severe steatosis observed in HCV-G3 may not result in increased IR.

7.2 Treatment

The goal of therapy is to cure HCV infection in order to: (1) prevent the complications of HCV-related disease (including progression to cirrhosis, decompensation of cirrhosis, HCC, HCV-related extrahepatic manifestations, and death), (2) improve the quality of life and removing stigma, and (3) prevent onward transmission of HCV [49]. For this purpose, all treatment-naïve and -experienced patients, who are willing to be treated and who have no contraindications for treatment, should receive antiviral therapy. In particular, treatment should be considered without delay in the following categories: patients with significant fibrosis (Metavir F2 or F3) or cirrhosis (including decompensated disease) and those with clinically significant HCV-related extrahepatic disease (e.g., symptomatic vasculitis associated with HCV-related cryoglobulinemia and HCV immune complex-related nephropathy), HCV recurrence after liver transplantation, at risk for faster progression of liver disease and individuals at high risk for transmitting HCV (e.g., PWID or men who have sex with men).

For several years, the only treatment options available for HCV-G3 were PegIFNα and RBV. In 2011, the first-generation protease inhibitors (telaprevir and boceprevir) were approved in combination with PegIFNα/RBV, increasing the SVR rates in patients with HCV genotype 1 [50, 51]. However, these agents added significant toxicity to the standard PegIFNα/RBV regimen and had suboptimal antiviral activity; thus, they were not approved for therapies of other HCV genotypes, including HCV-G3. Since 2013, newer, second-generation, all-oral DAAs regimens were approved, though only limited treatment options were initially available for patients with HCV-G3, becoming one of the most challenging subpopulations to treat. More effective, safer, and better-tolerated DAA therapies are nowadays recommended for HCV-G3 (Table 7.1), based on an increasing number of clinical trials assessing treatment efficacy in patients with HCV-G3 infection (Table 7.2).

7.2.1 Pegylated Interferon plus Ribavirin

The PegIFNα/RBV combination was the standard of care until the introduction of the first all-oral regimen including sofosbuvir (SOF) plus RBV [52, 53]. The recommended treatment was PegIFNα 2a (180 μg) or 2b (1.5 μg/kg) weekly plus RBV at a fixed dose of 800 mg daily, apart from patients with a body mass index beyond 25 or those who have baseline factors suggesting low responsiveness (IR, metabolic syndrome, severe fibrosis or cirrhosis, older age) should receive a weight-based dose of RBV, 15 mg/kg body weight/day for 24 weeks [54]. The overall SVR (undetectable HCV RNA level, 24 weeks after treatment discontinuation) rates with this combination were approximately 60% and were higher in non-cirrhotic patients (62.7%) than in cirrhotic ones (43%) [55]. The rapid virologic response (RVR), defined by HCV RNA undetectability of serum HCV—RNA at week 4 of treatment was found to be the most important factor predictive SVR [55, 56]. RVR occurred in 60% of HCV-G3 patients and was associated with high SVR rates [56]. In one large study, 86% of HCV-G3 patients who presented RVR subsequently achieved SVR, vs 48–52% of patients who did not present RVR [57], even when treatment was extended to 48 weeks. In another study, including 136 patients with advanced fibrosis treated with 180 μg weekly of PegIFNα2a and 800 mg daily of RBV, SVR rates were 48–42%, regardless of whether therapy was given for 24 or 48 weeks [58]. Therefore, prolongation of therapy with Peg-IFN and RBV in patients who do not achieve RVR does not seem to increase SVR rate. Peg-IFN and RBV combination has been associated with a wide array of adverse events that may require dose reduction or even discontinuation of treatment. Severe or even life-threatening side effects have been reported in 0.1%–1% of the patients. Based on known interferon toxicity several subgroups of patients with HCV infection are not eligible for interferon and ribavirin combination; psychosis, seizures, decompensated liver disease, pregnancy, and autoimmune hepatitis are important contraindications to interferon treatment.

Table 7.1 Current treatment options for patients with or without compensated cirrhosis infected with hepatitis C virus genotype 3 according to EASL or AASLD/IDSA recommendations

Regimen	Dosing (mg)	Treatment recommendations	
		EASL [49]	AASLD/IDSA [63]
SOF + DCV	400 + 60 *o.d.*	N.R.	[d]12 weeks in treatment-naïve patients without cirrhosis; [d]12 weeks in PegIFN/RBV-experienced patients without cirrhosis (RBV should be added if Y93H is present); [d]24 weeks with or without RBV in treatment-naïve patients with cirrhosis (RBV should be added if Y93H is present).
SOF + VEL[a]	400 + 100 *o.d.*	12 weeks in treatment-naïve or treatment-experienced[e] patients without cirrhosis.	12 weeks in treatment-naïve patients without cirrhosis; 12 weeks in PegIFN/RBV-experienced patients without cirrhosis (RBV should be added if Y93H substitution is present); 12 weeks in treatment-naïve patients with cirrhosis (RBV should be added if Y93H substitution is present); [d]12 weeks plus RBV in PegIFN/RBV-experienced patients with cirrhosis.
SOF + VEL + VOX[a]	400 + 100 + 100 *o.d.*	12 weeks in treatment-naïve and treatment-experienced[f] patients with cirrhosis.	12 weeks in PegIFN/RBV-experienced patients with compensated cirrhosis and DAA-experienced (including NS5A inhibitors) patients[b] with or without cirrhosis; [d]12 weeks in PegIFN/RBV-experienced patients without cirrhosis when Y93H is present; [d]12 weeks in treatment-naïve patients with compensated cirrhosis if Y93H is present.

(continued)

Table 7.1 (continued)

Regimen	Dosing (mg)	Treatment recommendations	
		EASL [49]	AASLD/IDSA [63]
GLE + PIBR[a]	100 + 40 *t.i.d*	8 weeks in treatment-naïve patients without cirrhosis; 12 weeks in treatment-naïve patients with cirrhosis and treatment-experienced[e] patients without cirrhosis; 16 weeks in treatment-experienced[e] patients with cirrhosis.	8 weeks in treatment-naïve patients without cirrhosis; 12 weeks in treatment-naïve patients with compensated cirrhosis; [d]16 weeks in treatment-experienced patients with or without compensated cirrhosis.
SOF + GZR + EBR[c]	400 + 100 + 50 *o.d.*	N.R.	12 weeks in treatment-experienced patients with cirrhosis.
SOF+(GLE + PIBR)[c]	400 *o.d.* + (100 + 40) *t.i.d*	12 weeks in DAA-experienced (protease inhibitor- and/or NS5A inhibitor-containing regimen) patients with or without cirrhosis who have predictors[g] of lower response.	N.R.

SOF: sofosbuvir, DCV: daclatasvir, VEL, PegIFN: pegylated interferon, velpatasvir, VOX: voxilaprevir, GLE: glecaprevir, PIBR: pibrentasvir, GZR: grazoprevir, EBR: elbasvir, NR: not recommended, DAA: direct-acting antivirals

[a]Denotes single-tablet combination

[b]For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended

[c]GRZ + EBR and GLE + PIBR are available in single-tablet combinations

[d]Recommended as an alternative treatment option

[e]Patients who failed PegIFN/RBV or SOF + PegIFN/RBV or SOF + RBV

[f]Including prior failure to protease inhibitor- and/or NS5A inhibitor-containing regimen

[g]Advanced liver disease, multiple DAA-based treatment courses, complex NS5A resistance profile

In summary, IFNα/RBV combination has been widely used worldwide for almost three decades. The peg-IFN/RBV can offer SVR in 60%–70% of the patients with HCV-G3. However, since the emergence of DAA agents, PegIFNα/RBV use has been removed from all guidelines and remains a therapeutic option only in countries that do not have access to DAAs.

7.2.2 Sofosbuvir plus Ribavirin

SOF (400 mg daily) plus RBV (1000 or 1200 mg daily in patients $<$75Kg and $\geq$ 75Kg, respectively) was the first interferon-free combination approved for

Table 7.2 Efficacy of direct-acting antivirals in patients with hepatitis C virus genotype 3 infection

Regimen	Trial [Ref]	Duration (weeks)	Treatment status	N		SVR (%)	
				Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic
SOF + RBV	POSITRON [53]	12	n	84	14	68	21
	FUSION [53]	12	e	38	26	37	19
		16	e	40	23	63	61
	FISSION [59]	12	n	183[a]		56[a]	
	BOSON [60]	16	n	70	21	83	57
		16	e	54	36	76	47
		24	n	72	22	90	82
		24	e	54	34	81	76
	VALENCE [62]	24	n	92	13	95	92
		24	e	98	47	87	62
	ASTRAL-3 [61]	24	n	156	45	90	73
		24	e	31	38	71	58
SOF + PegIFN+RBV	BOSON [60]	12	n	71	23	96	91
		12	e	52	35	94	86
	LONESTAR-2 [64]	12	e	13	13	83	83
	Esteban et al. [65]	12	e	14	8	93	88
SOF + LDV	Gane et al. [66]	12	n	21	4	71	25
SOF + LDV + RBV	Gane et al. [66]	12	n	20	6	100	100
	Gane et al. [66]	12	e	28	22	89	73
SOF + DCV	ALLY-3 [67]	12	n	75	19	97	58
	ALLY-3 [67]	12	e	34	13	94	69
	ENDURANCE-3 [68]	12	n	115		97	
	Hezode et al. [70]	12	n/e	23	36	96	68
	Hezode et al. [70]	24	n/e	44	147	98	88
	Sulkowski et al. [71]	24	n	14[b]		93[b]	

(continued)

Table 7.2 (continued)

Regimen	Trial [Ref]	Duration (weeks)	Treatment status	N		SVR (%)	
				Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic
SOF + DCV + RBV	ALLY-3+ [69]	12	n/e	6[c]	18	100[c]	83
	Hezode et al. [70]	12	n/e	2	7	100	57
	ALLY-3+ [69]	16	n/e	8[c]	18	100[c]	89
	Hezode et al. [70]	24	n/e	6	54	83	83
	Sulkowski et al. [71]	24	n	14[b]		86[b]	
SOF + VEL	ASTRAL-3 [61]	12	n	163	43	98	93
		12	e	34	37	91	89
	POLARIS-2 [72]	12	n/e[d]	89		97	
	POLARIS-3 [72]	12	n/e[d]		109		96
	POLARIS-4 [73]	12	e[e]	52[a]		85[a]	
SOF + VEL + RBV	Gane et al. [74]	24	e[f]	6	12	83	75
GLE + PIBR	ENDURANCE-3 [68]	8	n	157		95	
		12	n	223		95	
	SURVEYOR-II [76]	12	n		40		98
		12	e[g]	22		91	
		16	e[g]	22	47	95	96
SOF + VEL + VOX	POLARIS-2 [72]	8	n/e[d]	92		99	
	POLARIS-3 [72]	8	n/e[d]		110		96
	POLARIS-1 [73]	12	e[h]	78[a]		95[a]	
	POLARIS-4 [73]	12	e[e]	54[a]		96[a]	
SOF + EBR + GZR	C-SWIFT [78]	8	n	15		93	
		12	n	15	11	100	91
	C-ISLE [79]	12	n		24		96
		12	e		17		100

		16	e		18		94
SOF + EBR + GZR + RBV	C-ISLE [79]	8	n		23		91
		12	e		18		94

SOF: sofosbuvir, RBV: ribavirin, PegIFN: pegylated interferon, LDV: ledipasvir, DCV: daclatasvir, VEL: velpatasvir, GLE: glecaprevir, PIBR: pibrentasvir, VOX: voxilaprevir, EBR: elbasvir, GZR: grazoprevir; n: naïve, e: experienced

[a]Cirrhotic and non-cirrhotic patients combined

[b]Genotype 2/3 and cirrhotic/non-cirrhotic patients combined

[c]Patients with F3 fibrosis

[d]All patients were naïve to DAAs

[e]Previous DAA treatment, but not an NS5A inhibitor

[f]Previous DAA treatment, including 8–12 weeks of SOF/VEL with the addition or not of RBV or VOX

[g]Standard or PegIFN/RBV, or SOF plus PegIFN/RBV

[h]Previous NS5A inhibitor-containing DAA regimen

patients with HCV-G3. In the FISSION trial, 183 treatment-naïve patients (with or without cirrhosis) received SOF and RBV for 12 weeks, with 102 (55.7%) achieving SVR-12 (defined as HCV-RNA level below the threshold of quantification 12 weeks after the end of treatment) [59]. In the POSITRON trial, SVR-12 was achieved in 57/84 (68%) of treatment-naïve non-cirrhotic patients, although the response rate was only 3/14 (21%) in patients with cirrhosis [53]. Better outcomes are obtained by prolonging treatment: SOF and RBV for 16 weeks resulted in an SVR-12 of 83% (58/70) in non-cirrhotic patients and 57% (12/21) in those with cirrhosis [60]. For 24 weeks of therapy, cure rates ≥90% have been reported in treatment-naïve patients without cirrhosis and 73–92% in those with cirrhosis [61, 62].

In addition to short treatment duration and the presence of cirrhosis, prior treatment exposure is another major predictor of treatment failure with SOF plus RBV. In FUSION, 12 and 16 weeks of SOF/RBV yielded SVR-12 of only 36.8% (14/38) and 62.5% (25/40) in non-cirrhotic patients and 19.2% (5/26) and 60.9% (14/23) in cirrhotic patients who had previously failed PegIFNα-based therapy [53]. Again, an extension of treatment to 24 weeks appeared to improve SVR-12 in non-cirrhotic patients, although efficacy among patients with cirrhosis remains suboptimal ranging to 58–76% [60–62].

Taken these data together, the combination of SOF and RBV is effective in treatment-naïve, non-cirrhotic patients with HCV-G3. However, it requires a longer (16–24 weeks) treatment duration, which increases treatment cost and may carry a poorer risk profile. Moreover, even with extended treatment, results are questionable in hard-to-treat populations, such as in treatment-experienced patients and/or those with cirrhosis. Thus, due to several more effective therapies (Table 7.1), this regimen has been removed from the AASLD/IDSA and EASL HCV treatment guidelines [49, 63].

7.2.3 Sofosbuvir plus Pegylated Interferon plus Ribavirin

A more efficient approach is to use PegIFNα in a triple combination with SOF and RBV. In the BOSON trial, a 12-week SOF plus PegIFNα/RBV resulted in SVR-12 in 96% (68/71) of patients without cirrhosis and 91% (21/23) of those with compensated cirrhosis, outperforming both a 16-week (non-cirrhotic: 83%, cirrhotic: 57%) and a 24-week (non-cirrhotic: 90%, cirrhotic: 82%) combination of SOF/RBV [60]. In treatment-experienced patients without cirrhosis the SVR-12 was 94% (49/52), whereas it was 86% (30/35) in those with cirrhosis. Similar results were confirmed in two smaller studies [64, 65]. Even though SOF/PegIFNα/RBV appears to be efficacious, interferon-containing therapies have cumbersome contraindications and are associated with a significant burden of adverse events. Therefore, the current guidelines do not recommend this regimen, provided that more efficacious and better tolerated all-oral therapies have become available [49, 63].

7.2.4 Sofosbuvir/Ledipasvir with or Without Ribavirin

The addition of an NS5A inhibitor to SOF may be an alternative approach, aiming to shorten treatment duration and improve the overall cure rates. A single published trial has evaluated a 12-week combination of SOF plus LDV in treatment-naïve patients, yielding an SVR-12 of 71% (15/21) in non-cirrhotics, but only 25% (1/4) in patients with cirrhosis [66]. Addition of RBV has been shown to increase the virological response, with SVR-12 observed in 100% of both non-cirrhotic (20/20) and cirrhotic (6/6) HCV-G3 patients, whereas the corresponding rates in treatment-experienced patients were 89% (25/28) and 73% (16/22), respectively. To date, data concerning treatment outcomes with SOF/LDV in HCV-G3 remain limited, while newer more efficacious DAA combinations have been approved, some of which do not require RBV. Although SOF/LDV plus RBV is not a recommended treatment for HCV-G3 infection by international guidelines (Table 7.1), it could be a valuable alternative option in settings where preferred treatments are not available, particularly for treatment-naïve patients without cirrhosis.

7.2.5 Sofosbuvir plus Daclatasvir with or Without Ribavirin

In 2013, the approval of the pangenotypic NS5A inhibitor daclatasvir (DCV) represented a breakthrough towards a new era in the treatment of HCV-G3, due to the potential for interferon- and RBV-free DAA therapy. In the ALLY-3 study, non-cirrhotic patients receiving a 12-week combination of SOF/DCV achieved a high SVR-12 irrespective of past treatment exposure: 97% (73/75) in treatment-naïve patients, and 94% (32/34) in those who failed prior interferon-based therapies [67]. However, once again, cure rates in patients with cirrhosis (SVR-12: 58% and 69% in treatment-naïve and -experienced patients, respectively) lagged behind those of non-cirrhotic patients. Interestingly, the study also evaluated the relationship between NS5A resistance-associated variants (RAVs) at baseline (amino acid positions M28, A30, L31, Y93) and SVR-12, revealing significant associations. Specifically, the NS5A-Y93H polymorphism was detected in 13/147 patients, among whom 67% (6/9) without cirrhosis and 25% (1/4) with cirrhosis achieved SVR-12, compared to 98% (125/128), and 71% (24/34) of non-cirrhotics and cirrhotics without baseline NS5A-Y93H, respectively. More recently, the ENDURANCE-3 study has confirmed the high efficacy (SVR-12: 97%; 111/115) of 12-week SOF/DCV in treatment-naïve patients without cirrhosis [68].

Prolonging treatment is a valid option for increasing cure rates; however, RBV can be also added to the therapeutic regimen, aiming to maintain a short (12-week) treatment duration. The ALLY-3+ study determined no significant difference in the response rates by prolonging treatment with the triple SOF/DCV/RBV combination from 12 to 16 weeks in treatment-naïve and -experienced patients with F3 fibrosis ($n = 14$) and compensated cirrhosis ($n = 36$) [69]. Contrarily, in a real-world cohort of patients with HCV-G3 (treatment experienced: 72%, cirrhosis: 77%), an extension of the dual SOF/DCV combination from 12 to 24 weeks was associated with an

increase in SVR-12 from 68% to 88% in patients with cirrhosis, although no benefit could be observed in non-cirrhotics (98% vs 96%, respectively) [70]. Adding RBV to a 24-week regimen did not appear to improve cure rates, as confirmed in a phase 3 trial where a mixture of patients genotype 2 and HCV-G3 were included (SVR-12: 86% and 93% with and without RBV, respectively) [71].

In summary, data from small studies and real-world evidence have shown that SOF/DCV is well-tolerated and has high efficacy in non-cirrhotics after 12 weeks; however, the combination is associated with lower SVR-12 rates in experienced patients or patients with cirrhosis. Prolongation of treatment seems to improve SVR-12 rates. However, the approval of newer regimes that achieve higher SVR-12 after 8, 12, or 16 weeks in treatment-naïve or -experienced patients with or without cirrhosis, have led SOF/DCV combination not a first therapeutic option for HCV-G3 patients. Recent EASL guidelines do not include SOF/DCV as a treatment option for patients with HCV-G3, while the updated AASLD/IDSA guidance designates SOF/DCV as an alternative treatment option for treatment-naïve patients with HCV-G3, recommending baseline NS5A resistance testing in specific subgroups [63] (Table 7.1).

7.2.6 Sofosbuvir/Velpatasvir with or Without Ribavirin

In 2016, approval of the NS5A inhibitor velpatasvir (VEL) in combination with SOF ushered in the first fixed-dose, pangenotypic, all-oral DAA combination. In the ASTRAL-3 study, 98% (160/163) of treatment-naïve patients without cirrhosis and 93% (40/43) with compensated cirrhosis achieved SVR-12 after 12 weeks of SOF/VEL, whereas the corresponding rates in treatment-experienced patients were 91% (31/34) and 89% (33/37), respectively [61]. Moreover, among 25 patients with the Y93H NS5A RAV at baseline, 84% (21/25) achieved SVR-12, compared to 97% (225/231) of the patients without NS5A RAVs. Two additional trials, the POLARIS-2, and POLARIS-3 have confirmed the efficacy of the 12-week SOF/VEL combination in treatment-naïve patients, outlining response rates >95% (Table 7.2) [72].

More recently, data on the efficacy of SOF/VEL combination emerged for patients with previous failure to DAA regimens. In the POLARIS-4 trial, 52 patients who had previously failed a DAA regimen but not an NS5A inhibitor were treated with 12 weeks of SOF/VEL resulting in SVR-12 in 44 (85%) [73]. Furthermore, a 24-week combination of SOF/VEL plus RBV was assessed in 18 HCV-G3 patients with previous 8–12 week treatment, including SOF/VEL with the addition or not of RBV or the NS3/4A protease inhibitor voxilaprevir (VOX) [74]. The SVR-12 was 83% (5/6) in those without cirrhosis and 75% (9/12) in those with cirrhosis, highlighting a significant impact of baseline NS5A RAVs (SVR-12 82% in those with Y93H RAV vs 100% in those without). A randomized trial from Spain including HCV-G3 naïve and experienced patients with cirrhosis reported that the SOF/VEL/ RBV for 12 weeks achieved SVR in 96% of the patients [75].

Thus, the dual SOF/VEL combination given as one tablet daily with or without food, is a valuable 12-week, interferon- and RBV-free, treatment option for naïve

HCV-G3 patients without cirrhosis. The addition of a third drug (RBV or VOX) is justified, at least for those with cirrhosis.

7.2.7 Sofosbuvir/Velpatasvir/Voxilaprevir

Approved in 2017, this is the first pangenotypic, fixed-dose combination that includes medications from three different HCV antiviral classes: the NS5B polymerase inhibitor SOF, the NS5A inhibitor VEL and the NS3/4A protease inhibitor VOX (formerly GS-9857). The efficacy of the SOF/VEL/VOX combination is supported by data from the phase 3 POLARIS studies, which investigated 8 weeks of treatment in naïve patients (POLARIS 2 and 3) [72] and 12 weeks in treatment-experienced patients (POLARIS 1 and 4) [73] (Table 7.2). Among 92 non-cirrhotic DAA-naïve patients treated with 8 weeks of SOF/VEL/VOX in the POLARIS-2 trial, an SVR-12 was observed in 91 (99%) [72]. Similarly, in the POLARIS-3 trial, 106/110 (96%) patients randomized to 8 weeks of SOF/VEL/VOX achieved SVR-12, including 6/6 with Y93H detectable at baseline. Moreover, no patient receiving SOF/VEL/VOX with virologic failure developed RAVs.

The POLARIS-1 and POLARIS-4 trials included patients with HCV-G3, with or without compensated cirrhosis, who had previously failed a DAA-containing regimen, with or without an NS5A inhibitor [73]. A 12-week SOF/VEL/VOX combination yielded an SVR-12 of 96% (52/54) in patients who had previously failed a DAA (but not NS5A), and 95% (74/78) in those who had previously received a regimen containing an NS5A inhibitor.

Thus, SOF/VEL/VOX given as a single tablet, once daily with food, has high efficacy in naïve and experienced to DAAs patients with or without cirrhosis. It simplifies the treatment and fills the gap of therapeutic options for those who have previously failed a DAA regimen, either containing or not an NS5A inhibitor (Table 7.1) [49, 63].

7.2.8 Glecaprevir/Pibrentasvir

Another recent innovation in 2017 is the approval of the pangenotypic NS3/4A protease inhibitor glecaprevir (GLE) and NS5A inhibitor pibrentasvir (PIBR), administered as three fixed-dose combination pills. In treatment-naïve patients without cirrhosis GLE/PIBR achieved 95% SVR-12, regardless of whether it was administered for 8149/157) or 12 weeks (222/233) [68]. Both the 8- and 12-week regimens met non-inferiority criteria compared to the standard-of-care arm (12-week SOF/DCV; SVR-12: 97%), whereas baseline RAVs did not influence virological responses.

The efficacy and safety of 12 vs 16 weeks of GLE/PIBR in patients with prior treatment exposure (interferon or PegIFNα/RBV or SOF/PegIFNα/RBV) and/or compensated cirrhosis was assessed in SURVEYOR-II [76]. Among treatment-experienced patients without cirrhosis, SVR-12 was achieved by 91% (20/22) and

95% (21/22) of those treated for 12 and 16 weeks, respectively. In patients with cirrhosis, the SVR-12 was 98% (39/40) for treatment-naïve patients treated for 12 weeks and 96% (45/47) for those treatment-experienced patients receiving 16 weeks of therapy. Across all groups, A30 and Y93H baseline NS5A polymorphisms were the most frequent, detected in 12 (9.3%) and 8 (6%) patients, respectively. Seven out of 8 patients with Y93H and 10/12 with A30 baseline polymorphisms achieved SVR-12.

Interestingly, 12-week GLE/PIBR, a drug combination cleared by the hepatic metabolism, resulted in high SVR-12 (98%; 102/104) regardless of HCV genotype, presence of cirrhosis, or prior treatment exposure, in patients who had compensated liver disease (with or without cirrhosis) and severe renal impairment, including dependence on hemodialysis [77]. Serious adverse events occurred in 24% (25/104; most commonly pruritus, fatigue, and nausea); however, none were considered to be drug related by the study investigators. Based on these data, the 12-week fixed-dose combination of GLE/PIBR is recommended as the preferred option in patients with HCV-G3 and severe renal dysfunction [49, 63].

Therefore, in HCV-G3 GLE/PIBR taken orally once daily with food allows for shorter (8-week) treatment duration in naïve patients without evidence of cirrhosis. Pooled analysis of data from phase 2 and 3 clinical trials revealed that treatment should be extended to 12 weeks in naïve patients with compensated cirrhosis and in treatment-experienced without cirrhosis, whereas 16 weeks of therapy should be given for treatment-experienced cirrhotics [49, 63].

7.2.9 Sofosbuvir plus Grazoprevir/Elbasvir

The fixed-dose combination of elbasvir (EBR), an NS5A inhibitor, and grazopresvir (GZR), an NS3/4A inhibitor, in combination with SOF for 12 weeks is another recent addition to the armamentarium of DAA therapies, specifically focusing on the most difficult-to-cure population of treatment-experienced patients with compensated cirrhosis (Table 7.1). This regimen has been preliminarily assessed in the C-SWIFT trial, where 93% (14/15) of treatment-naïve non-cirrhotic patients treated for 8 weeks, 100% (14/14) of non-cirrhotics treated for 12 weeks, and 83% (10/12) of patients with cirrhosis treated for 12 weeks achieved SVR [78].

More recently, the efficacy of the SOF plus EBR/GZR combination, with or without RBV, for either 8 or 16 weeks of therapy, in treatment-naïve and -experienced patients with HCV-G3 and compensated cirrhosis was evaluated in the C-ISLE study [79]. The SVR-12 rates were 91% (21/23) and 96% (23/24) for treatment-naïve participants treated for 8 or 12 weeks, respectively. The SVR-12 rate among treatment-experienced patients (prior PegIFN/RBV failure) treated for 12 weeks was 100% (17/17), showing no evidence of additional benefit by the inclusion of RBV or extension of treatment to 16 weeks (in both cases, SVR-12 94%; 17/18). Importantly, response was not affected by baseline RAVs, obviating the need for viral resistance testing.

7.2.10 Treatment of HCV-G3 in Patients with Decompensated HCV Liver Disease

Patients with decompensated cirrhosis have an absolute contraindication to the use of PegIFNα, which may be associated with numerous and often severe side effects. Thus, interferon-free DAA regimens are the only viable treatment options for HCV-G3 patients with decompensated disease. Crucially, while SVR is often accompanied by an improvement, a subset of decompensated patients may not benefit or even experience a worsening in liver function tests [80, 81]. This has led to an open debate as to whether decompensated patients should be treated while wait-listed for liver transplantation or deferred until after liver transplant. Although robust predictors of long-term prognosis are still lacking, it appears that patients with a Model for End-stage Liver Disease (MELD) score $\geq$ 20 or severe portal hypertension complications are less likely to improve with DAAs and might have a better outcome when first transplanted [49]. Importantly, the protease inhibitor class should be avoided in the context of decompensated (Child-Pugh B and C) liver disease, as it is known to carry a poor risk profile for these patients.

In the ALLY-1 study, the SVR-12 was 83% in HCV-G3 patients with decompensated cirrhosis receiving SOF/DCV/RBV (600 mg/day, increased to tolerability) for 12 weeks [82], although a real-world study from the United Kingdom determined somewhat lower rates: 71% (75/105) and 60% (3/5), with or without RBV, respectively [81]. Contrarily, in a real-world Spanish cohort where most of the patients received a 24-week regimen with added RBV, the response rate was 94%, showing no difference between Child-Pugh A (92/98) and class B/C (31/33) disease [83].

The ASTRAL-4 study investigated the SOF/VEL combination given for 12 or 24 weeks in decompensated HCV-G3 patients, including an assessment of the impact of RBV on cure rates [84]. The SVR-12 rate for 12 weeks of SOF/VEL without or with RBV was 50% (7/14) and 85% (11/13), respectively. Contrarily, extension of treatment to 24 weeks without the addition of RBV did not improve the cure rate (50%; 6/12), outlining the continuous need for RBV in the difficult-to-treat population with decompensated cirrhosis.

Based on these data, SOF/VEL and SOF/DCV are recommended treatment options for HCV-G3 patients with decompensated cirrhosis [49, 63]. The addition of RBV (weight based for SOF/VEL; 600 mg initial dose, subsequently adjusted depending on tolerance for SOF/DCV) appears to optimize cure rates, provided that decompensated patients are both able to tolerate and have no contraindications to RBV (e.g., known hemolytic anemia). Importantly, no drug dose adjustments are required in the post-transplant setting, as no clinically relevant drug–drug interactions would be expected for co-administration with immunosuppressants.

7.2.11 Treatment of HIV/HCV-G3 Coinfected Patients

Due to the accelerated liver disease course seen with HIV coinfection, HIV/HCV coinfected patients are considered a high priority for treatment, regardless of fibrosis stage. In recent years, the advent of potent DAAs has been particularly transformative for HIV/HCV coinfected patients, closing the gap in SVR rates seen between mono- and coinfected patients in the PegIFNα/RBV era. Due to similar treatment outcomes [85–88], the DAA combinations recommended for HIV/HCV-G3 coinfected patients are the same as for HCV-G3 monoinfected patients. Therefore, HIV coinfected patients should no longer be viewed as a special population, at least as regards treatment efficacy. However, additional considerations remain in the management of this critical population, mainly due to the potential for severe drug-to-drug interactions with HIV antiretrovirals. For this reason, we recommend the use of regularly updated online resources, such as the drug interaction checker of the University of Liverpool, available at http://www.hep-druginteractions.org.

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