Angelos Hatzakis *Editor*

Hepatitis C: Care and Treatment

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Assessment of Liver Disease Severity

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Laurent Castera

1.1 Introduction

Staging of liver fibrosis and early detection of compensated cirrhosis are critical in the treatment decisions and surveillance of patients with chronic hepatitis C. Liver biopsy has been considered for decades as the "gold standard" for evaluation of hepatic fibrosis [1]. However, liver biopsy is an invasive procedure with rare but potentially life-threatening complications and prone to sampling errors. These limitations as well as the availability of direct-acting antiviral (DAA) agents have rapidly decreased the use of liver biopsy in viral hepatitis and fuelled the development of non-invasive methodologies for the assessment and staging of liver fibrosis.

Among the currently available non-invasive methods, there are two distinct approaches: (i) a "biological" approach based on the dosage of serum biomarkers of fibrosis and (ii) a "physical" approach based on the measurement of liver stiffness using either ultrasound- or magnetic resonance-based elastography techniques [2]. Although complementary, these two approaches are based on different rationale and conception: liver stiffness is related to elasticity, which corresponds to a genuine and intrinsic physical property of liver parenchyma, whereas serum biomarkers are combinations of several not strictly liver-specific blood parameters optimized to mimic fibrosis stages as assessed by liver biopsy [3]. Non-invasive methods are now used as first line in the routine management of patients with chronic hepatitis C and recommended by national and international guidelines [4–6].

We review herein the different methods that are currently available for the non-invasive evaluation of liver fibrosis in the management of patients with chronic hepatitis C before starting, during, and after antiviral therapy.

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1.2 Liver Biopsy: Advantages and Inconveniences

Histological staging of fibrosis is a combinatorial assessment of amount of fibrosis and architectural disorganization, based on semi-quantitative scoring systems, including the histological activity index [7], the Ishak score [8], and the METAVIR scoring system [9]. Simultaneous evaluation of necro-inflammation (portal tract inflammation, interface hepatitis, lobular inflammation) assesses whether fibrosis is the result of a past event that has stabilized or even regressed or is an ongoing process that may continue to worsen. Finally, apart from fibrosis, liver biopsy also detects associated lesions such as steatosis, steato-hepatitis, iron overload, and alcohol, which provide useful information for patient management and prognosis [10].

Liver biopsy has however well-known limitations: it is an invasive procedure associated with transient pain, anxiety, and discomfort in around 30% of cases [11–13] and rare but potentially life-threatening complications (hemorrhage in 0.3% of cases and mortality in 0.01%) [14]. Performing of biopsy by a trained physician, use of only a limited number of passes, and ultrasound guidance can significantly decrease the risk of complications, thereby enhancing the safety of biopsy.

The accuracy of liver biopsy to assess fibrosis has also been questioned, in relation to sampling errors and intra- and inter-observer variability that may lead to over- or under-staging. The size of the biopsy specimen, which varies between 10 and 30 mm in length and between 1.2 and 2 mm in diameter, represents 1/50,000 of the total mass of the liver and so carries substantial sampling error. Increasing the length of liver biopsy decreases the risk of sampling error [15]. However, cirrhosis may be missed on a single-blind liver biopsy in 10 to 30% of cases [16]. Finally, apart from the characteristics (sample size) of the liver biopsy, the degree of experience of the pathologist (specialization, duration of practice, and academic practice) may also have an influence on inter-observer agreement [17].

Except for cirrhosis, for which micro-fragments may be sufficient, a 25-mm-long biopsy is considered an optimal specimen for accurate evaluation, though 15 mm is considered sufficient in most studies [18]. In clinical practice, liver biopsy should always be performed only after carefully balancing risks of the procedure with potential benefits in terms of patient management.

1.3 Currently Available Non-invasive Methods

1.3.1 Biological Approach: Serum Biomarkers of Liver Fibrosis

Many serum biomarkers and evaluated for their ability to determine stage of liver fibrosis in patients with chronic hepatitis C [19–34]. They are summarized in Table 1.1: some are proprietary algorithms like the FibroTest®, while others are non-proprietary formula, using published models, based on routinely available laboratory tests.

Table 1.1 Currently available serum biomarkers for non-invasive evaluation of liver fibrosis in chronic hepatitis C (adapted from ref. [4])

- FibroTest® (Biopredictive, Paris, France) patented formula combining α-2-macroglobulin, γGT, apolipoprotein A1, haptoglobin, total bilirubin, age, and gender
- Forns index = 7.811 − 3.131 × ln(platelet count) + 0.781 × ln(GGT) + 3.467 × ln (age) − 0.014 × (cholesterol)
- AST to platelet ratio (APRI) = AST (/ULN)/platelet (10^9/L) × 100
- FibroSpectII® (Promotheus Laboratory Inc, San Diego, USA) patented formula combining α-2-macroglobulin, hyaluronate, and TIMP-1
- MP3 = 0.5903 × log PIIINP (ng/ml) − 0.1749 × log MMP-1 (ng/ml)
- Enhanced Liver Fibrosis (ELF) score® (Siemens Healthcare, Erlangen, Germany) patented formula combining age, hyaluronate, MMP-3, and TIMP-1
- Fibrosis probability index (FPI) = 10.929 + (1.827 × LnAST) + (0.081 × Age) + (0.768 × past alcohol use[a]) + (0.385 × HOMA-IR) − (0.447 × cholesterol)
- Hepascore® (PathWest, University of Western Australia, Australia) patented formula combining bilirubin, γGT, hyaluronate, α-2-macroglobulin, age, and gender
- Fibrometers® (Echosens, Paris, France) patented formula combining platelet count, prothrombin index, AST, α-2-macroglobulin, hyaluronate, urea, and age
- Lok index = − 5.56 − 0.0089 × platelet (10^3/mm^3) + 1.26 × AST/ALT ratio = 5.27 × INR
- Gotebörg University Cirrhosis Index (GUCI) = AST × prothrombin-INR × 100/platelet
- Virahep-C model = − 5.17 + 0.20 × race + 0.07 × age (years) + 1.19 ln (AST [IU/L]) − 1.76 ln (platelet count [103/mL]) + 1.38 ln (alkaline phosphatase [IU/L]
- Fibroindex = 1.738 − 0.064 × (platelets [10^4/mm^3]) + 0.005 × (AST [IU/L]) + 0.463 × (gamma globulin [g/dl])
- FIB-4 = age (years) × AST [U/l]/(platelets [10^9/l] × (ALT [U/l])$^{1/2}$
- HALT-C model = − 3.66 − 0.00995 × platelets (10^3/mL) + 0.008 × serum TIMP-1 + 1.42 × log (hyaluronate)

[a]Graded as 0–2

The practical advantages of analyzing serum biomarkers to measure fibrosis include their high applicability (>95%) and inter-laboratory reproducibility and their potential widespread availability (Table 1.2). However, none are liver specific—their results can be influenced by comorbid extra-hepatic conditions, and they require critical interpretation of results.

1.3.2 Physical Approach: Measuring Liver Stiffness

1.3.2.1 Transient Elastography

Transient elastography (TE) was the first commercially available ultrasound-based elastography method developed for the measurement of liver stiffness, using a dedicated device (FibroScan®, Echosens, Paris, France) [35]. TE measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver, which is directly related to tissue stiffness; the stiffer the tissue, the faster the shear wave propagates. The examination is performed on the right lobe of the liver through the intercostal space. The measurement depth is between 25 and 65 mm using the M probe (standard probe) and between 35 and 75 mm using the XL probe.

Table 1.2 Respective advantages and disadvantages of currently available non-invasive methods in patients with chronic hepatitis C (adapted from ref [4])

	Measurement of liver stiffness			
Serum biomarkers	Transient elastography	ARFI	2D SWE	MR elastography
Advantages				
• Good reproducibility • High applicability (95%) • No cost and wide availability (non-patented) • Well validated • Can be performed in the outpatient clinic	• Most widely used and validated technique: standard to be beaten • User-friendly (performed at bedside; rapid, easy to learn) • High range of values (2–75 kPa) • Quality criteria well defined • Good reproducibility • High performance for cirrhosis (AUROC >0.9) • Prognostic value in cirrhosis	• Can be implemented on a regular US machine • ROI smaller than TE but location chosen by the operator • Higher applicability than TE (not limited by ascites or obesity) • Performance equivalent to that of TE for significant fibrosis and cirrhosis	• Can be implemented on a regular • US machine • ROI can be adjusted in size and location and chosen by the operator • Real-time measurement • High range of values (2–150 kPa) • Good applicability • Performance equivalent to that of TE for significant fibrosis and cirrhosis	• Can be implemented on a regular MRI machine • Examination of the whole liver • Higher applicability than TE • High performance for cirrhosis
Disadvantages				
• Non-specific of the liver • Unable to discriminate between intermediate stages of fibrosis • Performance not as good as TE for cirrhosis • Cost and limited availability (proprietary) • Limitations (hemolysis, Gilbert syndrome, inflammation…)	• Requires a dedicated device • ROI cannot be chosen • Unable to discriminate between intermediate stages of fibrosis • Applicability (80%) lower than serum biomarker: (obesity, ascites, operator experience) • False positive in the case of acute hepatitis, extra-hepatic cholestasis, liver congestion, food intake, and excessive alcohol intake	• Unable to discriminate between intermediate stages of fibrosis • Units (m/sec) different from that of TE (kPa) • Narrow range of values (0.5–4.4 m/sec) • Quality criteria not well defined	• Unable to discriminate between intermediate stages of fibrosis • Quality criteria not well defined • Less well validated than TE and ARFI	• Requires a MRI facility • Less well evaluated than TE • More costly and time-consuming than TE • Failure due to claustrophobia or iron overload

ROI: region of interest

As suggested by the manufacturer, ten successful acquisitions should be performed on each patient. The median of these measurements is displayed and used for interpretation. Results are expressed in kilopascals (kPa) and range from 1.5 to 75 kPa with a normal value around 5 kPa [36].

Advantages to TE include the fact that it is a widely available point-of-care technique, with a short-time procedure (<5 min) and immediate results, that can be performed in the outpatient clinic by a nurse after a short learning curve (Table 1.2). Quality criteria are well defined, based on at least ten validated measurements and an interquartile range (IQR, reflects variations among measurements) of less than 30% of the median value (IQR/LSM ≤30%) [37]. It has been suggested that an even lower interquartile range should be used, especially in non-Asian patients with advanced fibrosis, but these criteria have not been independently validated [38].

Although TE analysis has excellent inter- and intra-observer agreement [39], its applicability (80%), when using the M probe [40], is not as good as that of serum biomarkers. The two main factors associated with decreased applicability are obesity and limited operator experience. The use of the XL probe has been proposed to overcome these limitations and has been shown to increase applicability to more than 95% in obese patients [41].

There are several confounding factors, such as transaminases flares, acute hepatitis, extra-hepatic cholestasis, or congestion, which may lead to overestimation of liver stiffness measurements, independent of fibrosis. Finally, food intake has been shown to be associated with the risk of overestimating liver stiffness values [42, 43]. Therefore, TE should be performed in patients fasting for at least 2 hours [4].

In summary, TE needs to be performed using a standardized protocol and with critically interpreted results, taking confounding factors into account.

1.3.2.2 Other Imaging Methods

Several other elastography techniques have been developed, either ultrasound-based such as point shear wave elastography/acoustic radiation force impulse (pSWE/ARFI) imaging and 2D shear wave elastography (2D SWE) or magnetic resonance-based such as MR elastography (MRE) [44].

pSWE/ARFI techniques, integrated in conventional ultrasound systems, use focused US "push" pulses to deform internal tissue and generate shear waves. Originally available in Siemens systems (Virtual Touch Quantification™ Acuson 2000, Siemens Healthineers, Erlangen, Germany), pSWE/ARFI methods are now integrated into their clinical ultrasound systems by most vendors [45]. Region of interest (ROI) localization can be chosen under B mode visualization. A single acoustic impulse is used to induce a shear wave within a small ROI (approximately 1.0 × 0.5 cm), and the velocity of shear waves is measured in meter/sec or kPa.

2D SWE, like pSWE/ARFI, is integrated in conventional ultrasonography systems, enabling the additional performance of elastography with the same probes as abdominal ultrasound. Originally available clinically in SuperSonic Imagine system (Aixplorer™, Supersonic Imagine, Aix-en-Provence, France), 2D SWE is

now integrated in their systems by several vendors. Multiple shear waves are induced using acoustic impulses. The size of the ROI can be increased to approximately 2 × 2 cm and shown as either single image or in real time. Velocity of stiffness can then be measured at varying locations within this ROI, and statistical quantities such as the mean, standard deviation, and minimum and maximum values of the 2D SWE or Young's modulus in kPa are calculated and displayed [44].

The major advantage of pSWE/ARFI and SWE is that they can be performed on commercial ultrasound machines with one probe in all patients, independent of body weight, as the ROI can be positioned manually at different depths in the liver (Table 1.2). However, these techniques also require more operator training and expertise. Quality criteria for the performance and interpretation of pSWE/ARFI and 2D SWE are not well defined by the manufacturers.

The advantages of MRE include its ability to analyze almost the entire liver and its applicability to patients with obesity or ascites. Failure rate is indeed low (6%) and is caused by claustrophobia, low hepatic signal related to iron overload, or not fitting into the MRE machine owing to obesity. However, MRE is too costly and time-consuming to be used in routine practice and is more suited for research.

1.4 Diagnostic Performances of Non-invasive Methods for Staging Liver Fibrosis

1.4.1 Endpoints

Two clinically relevant endpoints have been widely used in the literature to evaluate non-invasive methods: (1) Detection of significant fibrosis (METAVIR, F $\geq$2 or Ishak, $\geq$3), which is an indication for antiviral treatment in chronic hepatitis C. However, with the availability of DAA able to achieve sustained virological response (SVR) rates above 90% with limited side effects, significant fibrosis no longer represent an important decision-making endpoint in HCV-infected patients. (2) Detection of cirrhosis (METAVIR, F4 or Ishak, 5–6), which is an indication for specific monitoring of complications related to portal hypertension and to the increased risk of developing hepatocellular carcinoma (HCC) [46, 47].

1.4.2 Serum Biomarkers of Fibrosis

Diagnostic performances for significant fibrosis and cirrhosis of the different biomarkers are summarized in Table 1.3. To date, FibroTest®, APRI, and FIB-4 have been the most extensively studied in patients with chronic hepatitis C. In a meta-analysis from the developer [48], which pooled 6,378 subjects (with analysis of individual data in 3,282) with both FibroTest® and biopsy (3,501 HCV, 1,457 HBV, 267 NAFLD, 429 ALD, and 724 mixed), the mean standardized AUROC for diagnosing significant fibrosis was 0.84 (95% CI, 0.83–0.86), without differences between causes of liver disease. Another meta-analysis [49] analyzed results from

6259 HCV patients from 33 studies; the mean AUROC values from the APRI in diagnosis of significant fibrosis and cirrhosis were 0.77 and 0.83, respectively. When compared and validated externally in patients with viral hepatitis ($n = 1307$ patients with viral hepatitis) [50], the different patented scores (FibroTest®, Fibrometre®, Hepacore®) and non-patented scores (APRI) had similar performances for the diagnosis of significant fibrosis (AUROCs ranging from 0.72 to 0.78) and cirrhosis (AUROCS ranging from 0.77 to 0.86). Non-patented scores are cost-free, easy to calculate, and available almost everywhere.

1.4.3 Transient Elastography

The two index studies [51, 52], suggesting the interest of TE for the assessment of liver fibrosis, have been conducted in patients with chronic hepatitis C, and their results have been confirmed by many other groups since [50, 53–56] (Table 1.4). Several meta-analyses [57–61] have shown the better diagnostic accuracy of TE for cirrhosis (AUROCs 0.93–0.96) than for significant fibrosis (AUROCs 0.84–0.87). However, a meta-analysis based on individual data is still awaited. The diagnostic accuracy of TE is considered excellent for the diagnosis of cirrhosis with sensitivities and specificities of 83–87% and 89–95%, respectively. Actually, TE is better at ruling out, rather than ruling in, liver cirrhosis (with negative predictive value higher than 90%). Different cutoffs have been proposed for different liver diseases, depending on the distribution of fibrosis stages in different cohorts, but no consensus has been reached. In the meta-analyses, cutoffs ranged from 7.3 to 7.9 kPa for the diagnosis of significant fibrosis and from 13.0 to 15.6 kPa for the diagnosis of cirrhosis [58, 60–62]. However, the cutoff choice must also consider the pre-test probability of cirrhosis in the target population (varying from <1% in the general population to 10–20% in tertiary referral centers). For example, it has been shown that in a population with a pre-test probability of 13.8%, cirrhosis probability at a cutoff <7 kPa ranged from 0 to 3%, whereas at a cutoff >17 kPa, cirrhosis probability was 72% [50]. Thus, observer experience, patient factors, disease etiology, as well as pre-test probability of cirrhosis should be taken into account when measurement values are interpreted.

1.4.4 Other Imaging Methods

pSWE/ARFI performance has been evaluated in three meta-analyses reporting diagnostic accuracies of 84–87% for the diagnosis of significant fibrosis and of 92–93% for the diagnosis of cirrhosis [63–65]. Cutoffs ranged from 1.34 to 1.35 m/s for significant fibrosis and 1.80 to 1.87 m/s for cirrhosis. It should be stressed however that most studies included in these meta-analyses were based on small samples of heterogeneous populations and did not always use liver biopsy as reference. This said pSWE/ARFI like TE is better at ruling out than ruling in liver cirrhosis. Another meta-analysis comparing pSWE/ARFI with TE reported

Table 1.3 Diagnostic performance of serum biomarkers of fibrosis for significant fibrosis (F ≥ 2) and cirrhosis (F4) in patients with chronic hepatitis C

Biomarkers	Year	Patients (*n*)	F ≥ 2 (%)	F4 (%)	Cutoffs	AUROC	Se (%)	Sp (%)	CC (%)
FibroTest® [22]	2001	339	80		>0.48	0.87	75	85	46
Forns index [23]	2002	476	26		<4.2 >6.9	0.81	30–94	51–95	45
APRI [24]	2003	270	50	17	≤0.5 >1.5 <1.0 ≥2.0	0.80 0.89	41–91 57–89	47–95 75–93	44 72
FibroSpectII® [25]	2004	696	52		>0.36	0.83	77	73	75
MP3 [26]	2004	194	45	22[a]	<0.3 >0.4	0.82	35–65	85–96	NA
ELF® [27]	2004	1021/496[b]	40	12	0.102 NA	0.78 0.89	87 NA	51 NA	NA NA
Fibrometer® [30]	2005	598/503[b]	56		NA	0.89	80	84	82
FPI [28]	2005	302	48		≤0.2 ≥0.8	0.77	42–85	48–98	40–49
Hepascore® [29]	2005	211	57	16	≥0.5 >0.84	0.82 0.89	63 71	89 89	92 NA
Lok index [31]	2005	1141		38	<0.2 ≥0.5	0.81	40–98	53–99	52
GUCI [32]	2005	179		12	>0.1	0.85	80	70	NA
ViraHep-C [33]	2006	398	37		≤0.22 >0.55	0.83	51–90	54–90	52
Fibroindex [34]	2007	360	50		≤1.25 ≥ 2.25	0.83	30–40	97–97	35
FIB-4 [35]	2007	830		17[a]	<1.45 >3.25	0.85	38–74	81–98	68
HALT-C model [36]	2008	512		38	<0.2 ≥0.5	0.81	47–88	45–92	48

AUROC: area under ROC: curve; Se: sensitivity; Sp: specificity; CC: correctly classified: true positive and negative; NA not available

[a]F3F4

[b]HCV patients

Table 1.4 Diagnostic performance of TE for significant fibrosis (F ≥ 2) and cirrhosis (F4) in patients with chronic hepatitis C

Authors	Year	Patient (*n*)	F ≥ 2 (%)	F4 (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	CC (%)
Castera et al. [53]	2005	183	74	25	7.1 12.5	0.83 0.95	67 87	89 91	73 90
Ziol et al. [54]	2005	251	65	19	8.6 14.6	0.79 0.87	56 86	91 96	68 94
Arena et al. [56]	2008	150	56	19	7.8 14.8	0.91 0.98	83 94	82 92	83 92
Lupsor et al. [57]	2008	324	65	21	7.4 11.9	0.86 0.94	76 87	84 91	79 90
Degos et al. [52]	2010	913	62	14	5.2 12.9	0.75 0.90	90 72	32 89	57 87
Zarski et al. [58]	2012	382	47	14	5.2 12.9	0.82 0.93	97 77	35 90	64 88
Afdhal et al. [55]	2015	560[a]	67	15	8.4 12.8	0.73 0.90	58 76	75 85	70 80

AUROC: area under ROC curve; Se: sensitivity; Sp: specificity; CC: correctly classified: true positive and negative

[a]Validation cohort: HCV 92%; HBV 8%

comparable sensitivities and specificities for the assessment of liver fibrosis [66]. Thus, at present, pSWE/ARFI can be used with equivalent results to TE.

2D SWE has been evaluated in only a few studies, showing comparable or even superior results to TE for the diagnosis of significant fibrosis and comparable results for the diagnosis of cirrhosis [67, 68]. A meta-analysis, based on individual data in 1,340 patients with chronic liver disease, reported diagnostic accuracies of 86% for the diagnosis of significant fibrosis and 95% for cirrhosis [69]. The optimal cutoffs were 7.1 and 13.5 kPa, respectively. Again, 2D SWE is also better at ruling out than ruling in liver cirrhosis. When comparing 2D SWE to TE in this meta-analysis, no significant difference was found between the two methods if the quality criteria of TE were respected.

Studies comparing all three methods (TE, pSWE/ARFI, and 2D SWE) in the same patient population reported at least comparable results for all three methods with a slight superiority of 2D SWE for intermediate fibrosis stages [70, 71]. Thus, at present, 2D SWE can also be used with equivalent results to TE.

As for MRE, meta-analyses reported diagnostic accuracies of 93–98% for the diagnosis of advanced liver fibrosis (F≥3) with sensitivities of 85–92% and specificities of 85–96%, respectively [72, 73]. A limited number of studies have directly compared MRE to TE on small sampled heterogeneous populations and with conflicting results: one study reported comparable [74], whereas other reported superior results of MRE to TE [75, 76]. However, the widespread use of this method will depend on cost and availability.

1.5 Use in Clinical Practice in Patients with Chronic Hepatitis C

1.5.1 Before Starting Antiviral Treatment

The EASL clinical practice guidelines recommend that all patients with chronic hepatitis C should be assessed for liver disease severity before antiviral therapy using an algorithm combining non-invasive tests (TE and serum biomarkers) [4] (Fig. 1.1). This strategy has been validated in clinical practice [77, 78]. Identifying patients with cirrhosis or advanced (bridging) fibrosis is of particular importance, as the choice of the treatment regimen with novel DAA agents and the post-treatment prognosis depend on the stage of fibrosis. In patients with values in the range of liver cirrhosis, screening for portal hypertension and hepatocellular carcinoma (HCC) is also recommended without prior liver biopsy [46, 47]. In the case of unexplained discordance or suspected additional etiologies of liver disease, a liver biopsy is still recommended [4].

1.5.2 During Antiviral Treatment

A major advantage of non-invasive tests, compared with liver biopsy, is that they can be easily repeated over time in patients receiving antiviral therapy and that they could be used to monitor response to treatment and to evaluate fibrosis regression. However, the changing levels of ALT and inflammation of successfully treated HCV patients can confound results of TE or biomarkers. Indeed in a multicenter prospective study [79] that assessed liver stiffness kinetics at multiple time points during therapy (week 4 and 12) and afterward (week 24), liver stiffness decreased significantly with treatment among patients who did and did not achieve sustain viral eradication. These results suggest that the major component of the significant decrease observed in liver stiffness values is not just reversal of fibrosis but also reduction in liver injury, edema, and inflammation. Also significant variability of liver stiffness measurements, not related to disease progression or regression but rather to operator experience and patients BMI, has been reported [80]. Thus, monitoring liver stiffness or serum biomarkers during antiviral treatment is of limited clinical value and therefore not recommended [4].

1.5.3 After Antiviral Treatment

Several studies reported a significant decrease in liver stiffness and biomarkers values, compared with baseline values, in HCV patients who achieved SVR [79, 81–91], consistent with significant histologic improvement documented in studies of paired liver biopsies in these patients [92, 93]. It should be stressed however that these studies suffer from several methodological shortcomings: most are retrospective, with small sample size, including patients mainly treated with interferon-based therapies with a short follow-up and no paired liver biopsies.

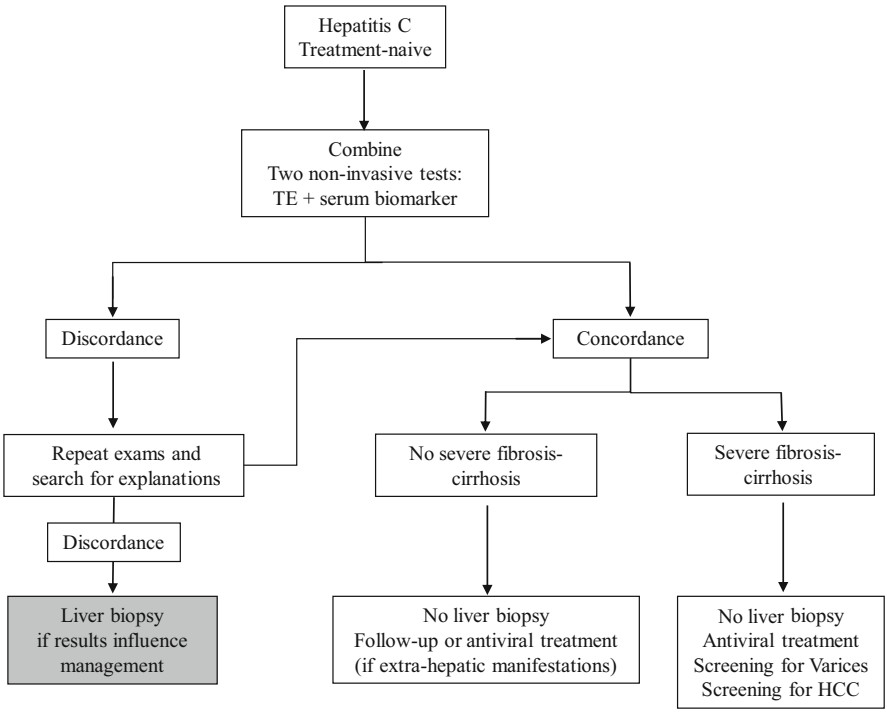

Fig. 1.1 Algorithm for the use of non-invasive tests in treatment-naive patients with hepatitis C (adapted from ref. [4])

Nevertheless, in a recent meta-analysis [94], based on 24 studies (10 with DAA) including a total of 2934 HCV patients, SVR was associated with a significant decrease in liver stiffness, particularly in patients with high baseline level of inflammation or patients who received DAA. Almost half the patients considered to have advanced fibrosis, based on TE, before therapy achieved post-treatment liver stiffness levels <9.5 kPa.

There are two important clinical questions about the use of non-invasive tests after antiviral treatment. First what is the evidence of fibrosis and particularly cirrhosis reversal by non-invasive tests? The reversal of cirrhosis has important consequences in that it may alter long-term prognosis particularly for HCC occurrence in HCV patients and change the approach to screening for HCC after SVR [95, 96]. This leads into the second question, which is what is the cutoff thresholds post-SVR for determination of decreased risk of liver-related outcomes? In a study that has examined reversal of cirrhosis in 33 HCV patients with cirrhosis with pre- and post-treatment liver biopsies and TE after SVR [97], there was reversal of cirrhosis by biopsy in 19 patients with 11 of the 19 being Metavir F3 and the remainder F1 or F2. Using a cutoff of 12 kPa, TE had a sensitivity of 61% and a specificity of 95%. The low sensitivity makes TE a poor tool to be utilized clinically as evidence of cirrhosis regression. Finally, the best timing for repeated assessment

of liver stiffness after therapy has not been established yet. In another study [98] from the same group in 38 HCV patients with cirrhosis with pre- and post-treatment liver biopsies and serum biomarkers (APRI, FIB-4, Forns score, GUCI, King score, Lok Index, and ELF) after SVR, none of these tests helped in predicting residual fibrosis. Therefore, liver biopsy remains the gold standard for this purpose, and routine use of non-invasive tests after SVR in patients without cirrhosis is not recommended, as it does not change clinical disease management [4]. In patients with cirrhosis, regression of fibrosis would improve outcome; however, high false-negative rates of non-invasive tests have been reported that do not justify a reduction in HCC surveillance in these patients.

1.6 Monitoring Disease Progression and Prognosis

There is substantial evidence indicating that liver stiffness, using TE, can be quite effective in detecting patients with a high risk of having (or not having) developed clinically significant portal hypertension (CSPH defined by a hepatic venous pressure gradient $\geq$10 mm Hg). A recent meta-analysis (based on 11 studies including 1451 patients) has confirmed the excellent performances of TE with a hierarchical summary AUROC of 0.90 and with sensitivity and specificity above 85% (sensitivity, 87.5%; 95% confidence interval [CI]: 75.8–93.9%; specificity, 85.3%; 95% CI: 76.9–90.9%) [99]. It is estimated that more than 90% of patients with a liver stiffness >20–25 kPa will have clinically significant portal hypertension [100]. Liver stiffness using TE is however less accurate for the prediction of esophageal varices (EV) than for CSPH [101]. In a recent meta-analysis [102] (based on 18 studies and 3644 patients), the diagnostic performances of TE for predicting EV and large esophageal varices (LEV) were not as good as for CSPH, with AUROCS of 0.84 and 0.78, respectively. Although the summary sensitivity for the prediction of the presence of EV and LEV was high (0.87 (95% CI: 0.80–0.92); 0.86 (95% CI: 0.71–0.94), respectively), specificity was much lower (0.53 (95% CI: 0.36–0.69); 0.59 (95% CI: 0.45–0.72), respectively) and less satisfactory. In order to increase the diagnostic accuracy, scores, like LSPS (LSM-spleen diameter to platelet ratio score), combining liver stiffness with parameters associated with portal hypertension, such as platelet count or spleen diameter by ultrasound, have been proposed [103, 104]. In 2015, the Baveno VI consensus on portal hypertension proposed using the combination of liver stiffness and platelet count (i.e., platelet count >150 g/L and LSM <20 kPa) to identify patients with early cirrhosis that could safely avoid screening endoscopy [105]. Interestingly, the performance of these criteria has been confirmed independently in various populations [106–108] and in two meta-analyses [109, 110]. All studies confirmed that about 20% of upper GI endoscopies could be safely avoided, missing less than 4% of patients with varices needing treatment. These recommendations represent a significant advance in the management of HCV patients with early cirrhosis and can be confidently applied in everyday practice. As for pSWE/ARFI and 2D SWE, given the very limited number of studies reporting on

their performance for detection of EV and LEV, no recommendation can be made [100].

The ability of liver stiffness, measured using TE, or of serum biomarkers to also predict clinical decompensation and survival in patients with chronic hepatitis C has been shown by several studies [89, 111, 112] as well as after viral eradication [113]. In one study that looked at the evolution of liver stiffness values over time in 1025 patients with chronic hepatitis C [89], the prognosis of patients with liver stiffness values between 7 and 14 kPa on inclusion was significantly impaired when an increase $\geq$ 1 kPa/year was observed. Thus, the potential of liver stiffness values for predicting clinical outcomes seems to be greater than that of liver biopsy; probably liver stiffness measures ongoing pathophysiological processes and functions that a biopsy cannot. Although most prognostic studies were performed with TE, other prognostic studies using point or 2D SWE are currently running, and the few that have been published report comparable prognostic capabilities [114–116].

1.7 Conclusions

Significant progress has been made over the past decade in non-invasive assessment of liver disease in patients with hepatitis C. Non-invasive tests are now ready for "prime time" to prioritize naive HCV patients for DAA therapies. The combination of TE and serum biomarkers is now routinely used as first-line evaluation, liver biopsy being reserved only in cases of unexplained discordance between TE and serum biomarkers results. Non-invasive test must be however interpreted critically by specialists according to clinical context and quality criteria. TE is currently the most used and validated technique for diagnosing cirrhosis (better at ruling out than ruling in). Its main limitation is its limited applicability in case of obesity and lack of operator experience. Monitoring of liver stiffness during antiviral treatment has limited value. In patients with HCV cirrhosis achieving SVR, follow-up with TE is not currently recommended but deserves to be further evaluated.

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Extrahepatic Manifestations of Hepatitis C Virus Infection

2

Anne Claire Desbois and Patrice Cacoub

2.1 Introduction

Approximately 130–170 million people are infected with hepatitis C virus (HCV) worldwide and 2.35% of the total world population. HCV has induced tremendous morbidity and mortality mainly due to liver complications (cirrhosis, hepatocellular carcinoma) and significant direct medical costs [1–3]. However, many extrahepatic manifestations have been reported to chronic HCV infection with increased related morbidity and mortality, including cardiovascular diseases, type 2 diabetes and insulin resistance, neurocognitive dysfunction, systemic vasculitis, B cell non-Hodgkin lymphoma and chronic kidney disease [4]. In large prospective cohort studies, up to two-thirds of patients with HCV infection experienced such extrahepatic manifestations [5].

2.2 HCV and Cryoglobulinemia Vasculitis (CryoVas)

HCV infection is associated with cryoglobulinemia in 30–50% of patients. Cryoglobulinemia is defined by the presence of circulating immunoglobulins that precipitate at cold temperature and dissolve with rewarming. CryoVas is related to HCV infection in 70–80% of cases, mostly associated with the type 2 IgM kappa

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mixed cryoglobulinemia. Mixed cryoglobulinemia lesions in HCV-infected patients are related to small vessel vasculitis induced by immune complex deposits.

2.2.1 Main Clinical Features

Clinical feature is variable, ranging from mild symptoms to life-threatening complications (glomerulonephritis, widespread vasculitis involving the central nervous system in particular) [5–8].

Fatigue is the main symptom, found in 80–90% of patients. Purpura (70 to 90%) is the most frequent cutaneous lesion. It begins at the lower limbs and may extend to the abdominal area and less frequently to the trunk and upper limbs. Cutaneous ulcers, Raynaud's phenomenon, and acrocyanosis are less frequent.

Sicca symptoms of either the mouth or eyes have been reported in 10–30% of patients. Although dry mouth and eyes are frequent in HCV-infected patients, a characterized Sjögren's syndrome, defined by the presence of anti-SSA or anti-SSB antibodies with positive histological findings, is uncommon.

Arthralgia (40–60%) is frequent and usually involves large joints. Arthralgia is bilateral and symmetric and involves more frequently fingers, knee, ankles and back [9]. Arthritis is uncommon (less than 10% of patients) and does not lead to articular deformation or destruction.

Neurologic manifestations (50–70%) include pure sensory polyneuropathy and mononeuritis multiplex. Polyneuropathy is frequently a distal sensory or sensory-motor neuropathy and usually presents with painful paresthesia. Motor deficit is less frequent and mainly affects the lower limbs. It often appears a few years after sensory symptoms. Central nervous system involvement is uncommon ($<10\%$) and may manifest as various symptoms such as stroke, epilepsy or cognitive impairment.

Renal manifestations affect from 20 to 40% of HCV-infected patients. They usually present as a proteinuria with microscopic haematuria and less frequently renal function impairment. Histological findings are most often an acute or chronic type 1 membranoproliferative glomerulonephritis with sub-endothelial deposits.

Other severe manifestations are very uncommon ($<5\%$). Cardiac involvement is associated with significant mortality. Cardiac complications include coronary vasculitis complicated by myocardial infarction, pericarditis, mitral valvular damages or congestive cardiac failure. Digestive involvement may lead to abdominal pains and gastrointestinal bleeding secondary to mesenteric vasculitis. The lungs are rarely involved (interstitial lung fibrosis, pleural effusion or pulmonary intra-alveolar haemorrhages).

2.2.2 Biological Surrogate Markers

The presence of cryoglobulinemia is confirmed by the detection of proteins which precipitate in the patient's serum maintained at 4°C during at least 7 days and

dissolve when heated at 37°C. A greater level than 0.05 g/L on two determinations is used to define a significant cryoglobulin level [6, 10]. To avoid false-negative results due to immunoglobulin cold precipitation, blood sampling should be carried immediately after blood is drawn using a thermostable device (37 °C). Serum should be kept warm. The detection of cryoglobulin should be repeated if first tests are negative although clinical features are suggestive of cryoglobulinemia vasculitis. Complement abnormalities such as decreased early components (C1q, C2, C4) and CH50, with normal C3 level, are suggestive of cryoglobulin. Electrophoresis and immunoelectrophoresis show either a polyclonal hypergammaglobulinemia or a monoclonal component.

To summarize, the presence of purpura, distal neuropathy and renal involvement associated with decreased C4 serum level, the presence of mixed cryoglobulinemia and a positive rheumatoid factor (RF) represent the main clinical and biological signs of CryoVas. If HCV infection is not already diagnosed, searching for HCV is mandatory.

2.2.3 Prognosis

In a large cohort of HCV-associated MC vasculitis ($n = 151$), poor prognosis factors were the presence of central nervous system involvement (HR 2.74), severe liver fibrosis (hazard ratio [HR] 5.31), kidney involvement (HR 1.91) and heart involvement (HR 4.2). The 3-year, 5-year, and 10-year survival rates were 86%, 75%, and 63%, respectively [9, 10]. The Five-Factor Score (FFS), based on five clinical items (proteinuria >1 gr/day, serum creatinine >140 μmol/L, cardiomyopathy, severe gastrointestinal and central nervous system involvements), was significantly associated with the outcome of patients. In multivariate analysis, severe fibrosis (HR 10.8) and the FFS (HR 2.49) were significantly associated with a poor prognosis [11]. The most common causes of death in HCV-CryoVas were infection, end-stage liver disease, cardiovascular disease and less frequently vasculitis or lymphoma/neoplasia [12, 13].

2.3 HCV and Kidney Disease

Although studies are heterogeneous, many data have been accumulated regarding the risk of chronic kidney disease (CKD) development in HCV-infected patients. On one hand, recent meta-analysis results of nine longitudinal studies (1,947,034 patients) demonstrated a relationship between HCV seropositivity and increased incidence of CKD (defined by incidence of stages 3–5 CKD or end-stage renal disease [ESRD]). The summary estimate for adjusted hazard ratio was 1.43 (95%CI 1.23; 1.63, $P = 0.0001$). In another meta-analysis, including 14 studies (336,227 patients), Park et al. reported that HCV-positive individuals had a 23% greater risk of having and/or developing CKD compared to uninfected individuals [14]. Consistently, in a nationwide cohort study including 293,480 Taiwanese residents among

which 37,152 were HCV infected, multivariate-adjusted regression revealed that HCV treatment (pegylated interferon plus ribavirin) was associated with a lower risk of ESRD after an 8-year follow-up (HR 0.15; 95% CI 0.07 to 0.31; $p < 0.001$) [15]. These data were further confirmed by other recent studies [16]. Using proteinuria as a marker of CKD, Fabrizi et al. found in their meta-analysis, including 6 studies and 107,356 patients, that HCV-positive serology was an independent risk factor for proteinuria with an adjusted OR of 1.508 (95%CI 1.19; 1.89, $P = 0.0001$) [17].

On the other hand, eight studies with cross-sectional design ($n = 788{,}027$ patients) did not find a significant relationship between positive HCV serologic status and increased prevalence of CKD (mainly defined by low eGFR < 60 ml/min/1.73 m^2), with adjusted OR of 1.16 (95%CI 0.98; 1.33, P = NS) [17]. In a retrospective cohort consisting of 71,528 veterans, after a 6-year follow-up, 2,589 individuals with recently seroconverted HCV were less likely to develop advanced CKD after controlling for traditional risk factors (HR 0.86; 95%CI 0.79, 0.92).

Renal manifestations are also often reported in HCV-CryoVas patients (20–35%) and are related to acute or chronic type 1 membranoproliferative glomerulonephritis (MPGN) with sub-endothelial deposits. A large case-control study, carried out among US male veterans hospitalized between 1992 and 1999, identified 34,204 patients who were hospitalized with HCV infection (cases) and 136,816 randomly selected patients without HCV infection (controls). There was a greater proportion of MPGN among patients with vs. those without HCV infection (0.36% vs. 0.05%, $p < 0.0001$). The most frequent presentation is proteinuria with microscopic haematuria and a variable degree of renal insufficiency. Early serum complement component levels (C1q, C4) are very low. Morphological features are characterized by important monocyte infiltrates with double contours of the basement membrane and large, eosinophilic and amorphous intra-luminal thrombi. Indirect immunofluorescence shows intra-glomerular sub-endothelial deposits of IgG, IgM and complement components.

2.4 HCV and Diabetes

Many studies have evaluated the association between HCV chronic infection, insulin resistance and diabetes mellitus. The abnormalities of carbohydrate metabolism, including hyperinsulinemia and insulin resistance, known to be per se related to chronic hepatic diseases, were the rationale for speculation on the relationship between HCV and glucose abnormalities. Insulin resistance is an often undetected condition, commonly coexisting with obesity and metabolic syndrome and possibly progressing to type 2 diabetes. HCV-related type 2 diabetes mellitus may arise from a complex interaction between insulin resistance, steatosis and inflammatory processes. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection were first published in the early 1990s. More recently, larger epidemiologic studies gave more in-depth analyses of the relationship between HCV chronic infection and glucose abnormalities. This tight association was confirmed in

both directions by the increased rates of HCV infection markers in type 2 diabetes/insulin resistance patients and the high rates of glucose abnormalities in HCV-infected patients. HCV infection is significantly associated with diabetes and insulin resistance compared with healthy volunteers and patients with hepatitis B virus infection. Glucose abnormalities are associated with advanced liver fibrosis, lack of sustained virological response to interferon alfa-based treatment and a higher risk of HCC development. However, the efficacy of antidiabetic treatment in improving the response to antiviral treatment and in decreasing the risk of HCC remains to be clarified [18].

2.5 HCV and Cardiovascular Disease

Recent studies have provided important data on the tight link between HCV infection and cardiovascular events. In a cohort of 1323 HCV-infected patients with biopsy-proven cirrhosis (Child-Pugh class A) receiving anti-HCV treatment before or after inclusion (with interferon then with direct antiviral agents), a sustained virological response (SVR) was associated with a lower risk of cardiovascular events (HR, 0.42; 95% CI, 0.25–0.69; $P = 0.001$). SVR affected overall mortality and death from liver-related and non-liver-related causes [19]. A literature review confirmed these results [20]. Subjects with HCV chronic infection have an increased prevalence of carotid atherosclerosis and increased intima-media thickness compared to healthy controls or those with hepatitis B or non-alcoholic steatohepatitis. Active chronic HCV infection appears as an independent risk factor for ischemic cerebrovascular accidents and ischemic heart disease. The risk of major cardiovascular events in HCV-infected patients was independent of the severity of the liver disease or the common cardiovascular risk factors. Considering the increased prevalence and prognostic relevance of cardiovascular events, it is opportune to include these harmful manifestations among HCV extrahepatic manifestations. Therefore, a non-invasive screening for cardiovascular alterations (Doppler ultrasound studies, EKG) is recommendable at the first patient's assessment followed by careful monitoring during follow-up [21].

2.6 HCV and Cancer

HCV-associated lymphomas mainly include B cell histological subtypes (B-NHL). Low-grade marginal zone lymphoma (particularly those of splenic origin) and de novo or transformed diffuse large B cell lymphoma are the most common subtypes, followed by follicular lymphoma. Large studies showed an overall increased risk of B-NHL in patients with chronic HCV infection when compared with HCV-negative controls (RR 2.4; 95% CI: 2.0–3.0). Lymphomas usually occur after a long period of HCV infection (more than 15 years). Transformed diffuse large B cell lymphomas are more common in HCV patients as compared to non-infected people.

Pathophysiological mechanisms of lymphoma transformation in HCV are not completely understood. It is now well established that chronic stimulation by HCV antigens leads to stimulation of antigen-specific B cell clones and likely represents the main driving mechanism in marginal zone lymphoma and, to some extent, in transformed DLBCL deriving from marginal zone lymphoma [22–24]. Couronné et al. also propose an alternative pathway of transformation based on direct HCV infection of B cells, especially in the HCV-positive de novo DLBCL subgroup [23]. It is most likely that additional genetic events are necessary for HCV-associated B cell transformation (such as NOTCH mutations). In a cohort of HCV-infected patients with DLCB, multivariate analysis showed that only International Prognostic Index score and antiviral treatment (sofosbuvir/ledipasvir) were independently correlated with a better disease-free survival [25].

Other studies found an association between HCV infection and cancer occurrence. From the large US Chronic Hepatitis Cohort Study (CHeCS), Allison et al. showed that the incidence of the cancers was significantly higher among HCV-infected patients: liver (RR, 48.6 [95% CI, 44.4–52.7]), pancreas (2.5 [1.7–3.2]), rectum (2.1 [1.3–2.8]), kidney (1.7 [1.1–2.2]), non-Hodgkin lymphoma (NHL) (1.6 [1.2–2.1]), and lung (1.6 [1.3–1.9]). The mean ages of cancer diagnosis and cancer-related death were significantly younger among HCV cohort patients compared to the general population for many cancers [26].

2.7 HCV, Fatigue and Depression

Fatigue is often reported in HCV-infected patients [4, 27, 28]. In a large prospective study, 19% of 1,614 HCV-infected patients fulfilled the main diagnostic criteria of fibromyalgia (fatigue, arthralgia and myalgia) [5]. A fatigue, with or without a fibromyalgia, was the most frequent extrahepatic manifestation (35–67%). Many factors were independently associated to fatigue as older age, female gender and the presence of arthralgia/myalgia as well as neuropsychological factors. There was no link with alcohol consumption, HCV genotype or viral load, the presence of a cryoglobulin and a thyroid dysfunction. Of note, after IFN-based treatment, only the group of patients with a sustained virological response had a positive impact on fatigue. The benefit of treatment on arthralgia/myalgia was found in about 50 percent of patients, independent of the virological response. Treating the underlying disease with newly developed direct-acting antivirals often improves the perceived fatigue [29].

Depression is a frequent disorder, which has been reported in one-third of patients with HCV infection and has an estimated prevalence of 1.5 to 4.0 times higher than that observed in patients with chronic hepatitis B virus infection or the general population. HCV seems to play a direct and indirect role in the development of depression. Impaired quality of life and increasing health-care costs have been reported for patients with HCV infection with depression. Treatment-induced HCV clearance has been associated with improvement of depression and quality of life [30].

Finally, HCV has been reported to be associated with cognitive impairment. Fatigue, sleep disturbance, depression and reduced quality of life are commonly associated with neurocognitive alterations in patients with non-cirrhotic chronic HCV infection, regardless of the stage of liver fibrosis and the infecting genotype. These manifestations occur in the absence of structural brain damage [31].

2.8 HCV and Other Manifestations

Sicca symptoms of either the mouth or eyes have been reported in 10% to 30% of HCV-infected patients, whereas less than 5% of patients with a defined Sjögren's syndrome (SS) are HCV-positive [27]. Although sicca symptoms are frequent in HCV-infected patients, a characterized Sjögren's syndrome defined by the presence of anti-SSA or anti-SSB antibodies and a typical salivary gland histology is uncommon. A large cohort study of 137 defined Sjögren's syndrome patients compared patients with HCV infection to those with a primary form. HCV-infected patients with Sjögren's syndrome were more frequently older male, with vasculitis, peripheral neuropathy and neoplasia. They also had a different biological pattern, i.e. more frequently positive RF, cryoglobulinemia and less frequently anti-SSA or SSB antibodies [32, 33]. Interestingly, only 23% of HCV-associated Sjögren's syndrome patients had positive anti-ENA. The detection of HCV-RNA and HCV core antigen in epithelial cells of HCV patients with Sjögren's syndrome and the development of Sjögren's syndrome like exocrinopathy in transgenic mice carrying the HCV envelope genes support a direct impact of HCV itself on the development of sialadenitis [34, 35].

2.9 How to Treat HCV-CryoVas and Other Extrahepatic Manifestations

HCV-CryoVas manifestations improve or disappear when a sustained clearance of HCV is achieved [i.e. SVR]. Before 2012, pegylated interferon (PegIFN) plus ribavirin for 12 months led to SVR in 50–60% of HCV-CryoVas patients [17, 18]. Relapses for HCV infection after responding to antiviral therapy were usually associated with a relapse of the vasculitis with the return of viraemia [19]. The use of antiviral therapy including PegIFN, ribavirin and a direct-acting antiviral (DAA) (NS3/4A protease inhibitor) led to greater SVR rates (65–70%) in HCV-CryoVas patients with genotype 1 infection [36, 37]. However, such combination should be given for a long time (48 weeks) and was complicated with serious adverse events [36].

The second-generation DAAs allow to treat patients with interferon-free combinations and are associated with high (>95%) SVR rates and relatively few side effects [38]. In the first prospective, open-label trial, including 24 HCV-CryoVas patients (50% genotype 1, 50% cirrhosis) treated with sofosbuvir plus ribavirin, a SVR was achieved in 74% of patients and clinical complete remission in 87.5% at

week 12 after the end of treatment [39]. The cryoglobulin level decreased from 0.35 to 0.15 g/L. In a retrospective case series, including 12 HCV patients (50% cirrhosis, 67% genotype 1, 7 patients with kidney involvement) treated with sofosbuvir plus simeprevir (67%) or ribavirin (33%), the rate of SVR was 83% at 12 weeks after the end of treatment [40]. Cryoglobulin levels disappeared in 4/9 patients. Two patients had serious adverse events. Gragnani et al. have reported 44 consecutive patients with HCV-CryoVas [genotypes 1 ($n = 23$), 2 ($n = 13$), 3 ($n = 5$) and 4 ($n = 3$)] [41]. Patients were treated with sofosbuvir-based treatments. All patients had negative HCV viraemia at week 24 post-treatment; all had a clinical response of vasculitis. The mean cryocrit level fell from 7.2% to 1.8. Only mild adverse events were reported in 59% of patients, except for one patient with ribavirin-related anaemia requiring blood transfusion. Kondili et al. reported the disappearance or improvement of more than 50% of CryoVas symptoms in 84% of patients after DAA [42]. A study from Canada ($n = 11$) reported a full or partial clinical response of CryoVas in 91% and a complete or partial immunological response in 81% [43]. A full or partial renal response was noted in 80%. A serious adverse event was reported in only 12%.

Despite the positive impact of effective antiviral treatments on HCV vasculitis symptoms, immunosuppression still remains a major treatment option in the case of severe CryoVas manifestations (severe renal impairment, skin necrosis, gut or CNS involvement, etc.) or in patients with failure or contraindication to antivirals.

Rituximab was shown to be more efficient than conventional immunosuppressive treatments (i.e. glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis) or placebo [44, 45]. Addition of rituximab to antivirals (with PEG-IFN) led to a shorter time to clinical remission, better renal response rate and higher rates of cryoglobulin clearance [46, 47].

International guidelines [48] recommend to treat HCV-infected patients with severe extrahepatic manifestations such as vasculitis. Multidisciplinary consensus on the management of HCV extrahepatic manifestations recommends considering IFN-free DAAs as first-line treatment for HCV-CryoVas patients that do not need life-threatening measures [49]. Early viral eradication is recommended. The choice of IFN-free DAA combination depends on general criteria for the treatment of HCV infection (i.e. the presence of kidney disease, ischemic tissue lesions, anaemia, lymphoproliferative disease). Accurate evaluation of the kidney function is mandatory for the choice of DAA treatment [50].

In the case of HCV-CryoVas needing life-threatening measures, the combination of IFN-free DAA and immunosuppressive therapy can be allowed. The choice of immunosuppressive therapy always considers the severity of vasculitis, the degree of HCV-related liver damage and the possible drug-drug interactions. Immunosuppressive therapies include glucocorticoids, rituximab, cyclophosphamide and plasmapheresis. Such therapies may also be useful in patients with persistent vasculitis manifestations despite HCV eradication. The persistence of laboratory abnormalities alone (i.e. cryoglobulinemia) without clinical symptoms after successful antiviral therapy does not justify therapy. Persistent CryoVas manifestations despite a SVR should lead to search for the presence of B cell lymphoma.

In summary, HCV infection is strongly associated to extrahepatic manifestations, including cardiovascular diseases, type 2 diabetes and insulin resistance, neurocognitive dysfunction, systemic vasculitis, B cell non-Hodgkin lymphoma and chronic kidney disease. The treatment of HCV-associated extrahepatic complications has much changed with the recent emergence of DAA enabling high cure rates with a good safety profile. The efficacy of new DAA represents major changes in clinical practice, since new antivirals provide for the first time safe and definitive treatment of such complications for many patients.

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Overview of Treatment Recommendations and Pretreatment Assessment

3

Maria Buti

The introduction of direct-acting antivirals (DAAs), drugs that target specific non-structural proteins of hepatitis C virus (HCV) and disrupt viral replication, has revolutionized therapy for HCV infection [1, 2]. Combination regimens of all-oral DAAs are highly effective, well-tolerated, and the treatment of choice for most HCV-infected patients, achieving HCV elimination in almost all cases. The goal of antiviral therapy in patients with chronic HCV is to eradicate HCV RNA, which is predicted by attainment of sustained virologic response (SVR), defined as an undetectable RNA level 12 weeks following completion of therapy. SVR is associated with a 97–100% chance of testing HCV RNA negative during long-term follow-up and therefore can be considered to indicate infection cure [1–3].

Patients who are cured of HCV experience numerous health benefits, including a decrease in liver inflammation and a reduction in the progression of liver fibrosis [4]. More important, patients who achieve SVR have lower all-cause mortality, liver-related death, liver transplantation requirements, hepatocellular carcinoma (HCC) rates, and liver-related complications, even those with advanced liver fibrosis [4–7]. Cure of HCV infection also reduces symptoms and deaths from severe extrahepatic manifestations, including mixed cryoglobulinemia, a condition affecting 10–15% of HCV-infected patients [8, 9], and other diseases related to HCV infection such as non-Hodgkin lymphoma and other lymphoproliferative disorders [10]. Lastly, patients who achieve SVR have a substantially improved quality of life, including physical, emotional, and social health [11]. Because of the many benefits associated with successful HCV treatment, clinicians treating HCV-infected patients with antiviral therapy should attempt to achieve SVR, preferably early in the course of chronic infection, before the development of severe liver disease and other related complications.

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Another relevant consideration is that persons who have successfully achieved a virologic cure no longer transmit the virus to others. This is particularly important in an infection without a specific vaccine. Therefore, successful treatment of HCV infection benefits public health. Several health models have shown that even modest increases in successful HCV treatment among persons who inject recreational drugs can decrease the prevalence and incidence of this disease [12, 13]. However, to guide the implementation of hepatitis C treatment as a prevention strategy, further studies are needed to define the best candidates for treatment to stop transmission, and the cost-effectiveness of the strategies when used in target populations.

3.1 Treatment Recommendations

All patients with virologic evidence of chronic HCV infection, that is, detectable HCV RNA over a 6-month period, should be considered for treatment. All guidelines agree on the recommendation to treat patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapies. Due to the initially high cost of these all-oral antiviral regimens, public health authorities in some countries have prioritized or even restricted treatment to patients with advanced fibrosis. Nonetheless, several studies have suggested that these regimens, even at their introductory high cost, are cost-effective for many populations, including patients with mild fibrosis [14, 15].

3.2 Hepatic Manifestations of Chronic HCV infection

Recent studies have reported the benefits of treatment at earlier fibrosis stages (e.g., no fibrosis or mild fibrosis). In a long-term follow-up study including 820 patients with fibrosis stage F0 or F1 (Metavir score), the 15-year survival rate was significantly better in those who experienced SVR than in those whose treatment had failed and in untreated patients (93%, 82%, and 88%, respectively; $P = .003$) [16]. The results of this study and others are in favor of earlier treatment initiation.

In patients with advanced liver fibrosis or cirrhosis (Metavir stage F3 or F4), the risk of developing complications of liver disease such as hepatic decompensation or HCC is substantial and may occur in a relatively short timeframe. The risk of decompensation, including HCC, ascites, jaundice, bleeding, encephalopathy, and death, ranges from 3.9% to 7.5% annually [17–19]. Several studies have demonstrated that hepatitis C therapy and achievement of SVR in this population results in considerable decreases in hepatic decompensation events, HCC, and liver-related mortality [6, 7, 20–27]. In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved SVR, compared with patients with similarly advanced liver fibrosis who did not achieve SVR, had a lower liver transplantation requirement (hazard ratio [HR], 0.17; 95% confidence interval [CI], 0.06–0.46), and lower liver-related morbidity and mortality (HR, 0.15; 95%

CI, 0.06–0.38) and HCC (HR, 0.19; 95% CI, 0.04–0.80) [27]. Of note, persons with advanced liver disease also require long-term follow-up and HCC surveillance, regardless of the treatment outcome.

3.3 Persons at Greater Risk for Rapidly Progressive Fibrosis and Cirrhosis

Fibrosis progression is variable across different patient populations and within the same individual over time. However, certain factors, such as coinfection with other viruses (e.g., hepatitis B virus [HBV]) and prevalent coexistent liver diseases (e.g., nonalcoholic steatohepatitis) are well-recognized contributors to accelerated fibrosis progression.

HIV coinfection accelerates fibrosis progression in HCV-infected persons [20], although control of HIV replication and restoration of CD4+ cell counts may mitigate this to some extent [21]. In a prospective study including 282 HIV/HCV-coinfected patients with 435 paired biopsies, one-third of patients showed fibrosis progression of at least one Metavir stage at a median of 2.5 years [20]. In addition, HIV coinfection shortens the survival of patients with decompensated liver disease. In some countries, these patients have a more restricted access or lack of access to liver transplantation, and the poor outcomes following transplantation highlight the need for treatment in this population, regardless of the current fibrosis stage [22].

Patients with HBV/HCV coinfection and detectable viremia of both viruses are at an increased risk for disease progression, decompensated liver disease, and the development of HCC. These patients should be considered for HCV and HBV therapies. Viral interference often occurs in HBV/HCV-coinfected patients, and HCV suppresses HBV. Thus, when treating HCV with antiviral drugs, and coinciding with HCV suppression, a rebound in HBV viral load can take place. Periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. In such cases, HBV infection should be treated as recommended for HBV monoinfection [2].

3.4 Extrahepatic Manifestations of Chronic HCV Infection

Chronic hepatitis C is associated with mixed cryoglobulinemia and lymphoproliferative disorders. Mixed cryoglobulinemia produces arthralgia, fatigue, palpable purpura, renal disease, neurologic disease, and reduced complement levels [28]. The clinical manifestations reduce survival and negatively impact on quality of life. Several studies with DAAs in patients with mixed cryoglobulinemia have shown that antiviral efficacy is the same as in patients with chronic hepatitis C and that extrahepatic manifestations improve or even resolve in this population.

Several non-hepatic manifestations have been related to, or more frequently observed in, HCV-infected persons, such as fatigue, diabetes mellitus, and porphyria

cutanea tarda. Successful antiviral treatment has been associated with improved markers of insulin resistance and a greatly reduced incidence of new-onset type 2 diabetes and insulin resistance in HCV-infected patients [29]. In addition, antiviral therapy may prevent progression to diabetes in patients with prediabetes who have HCV and may reduce renal and cardiovascular complications in patients with established diabetes who have HCV [30].

Fatigue is a common symptom in patients with chronic HCV infection. Patients who achieve SVR show a substantial decrease in the frequency and severity of fatigue, and improvements in the overall health-related quality of life and work productivity [31].

Patients with porphyria cutanea tarda often have HCV infection, particularly those with cirrhosis; a 50% prevalence of HCV infection has been reported in this population [32]. Porphyria cutanea tarda manifestations improve during IFN therapy [33], and it is likely that the same will happen with DAAs. However, the currently available data do not suffice to determine whether treating HCV infection with DAAs and achieving SVR improves porphyria cutanea tarda.

3.5 Therapy to Prevent HCV Transmission

Currently, there is no specific vaccine against HCV. However, treatment with DAAs can be used to prevent or at least control infection, and to avoid transmission and new cases of infection.

3.6 Health Care Workers

Health care workers infected by HCV and with a high viral load are under restrictions to perform procedures that may lead to exposure [34]. By treating these persons, the risk of HCV transmission has the potential to dramatically decrease HCV incidence and prevalence.

3.7 Injection Drug Users

Recreational use of injection drugs is the most common risk factor for HCV infection in Western countries. HCV seroprevalence in this population is 10–70% [35]. Injection drug use also accounts for most new HCV infections (approximately 70%) and is the key factor for maintaining the epidemic. HCV therapy with DAAs is highly effective in this population and SVR rates are similar to those of non-users. However, the reinfection rates are high 6.1–27.2/100 person-years, and they increase with active or ongoing drug use (6.44/100 person-years) [36].

3.8 HIV-infected Men Who Have Sex with Men

HIV-infected men who have sex with men, together with injection drug users, have the highest incidence of acute infection and are considered HCV "reservoirs." Recognition and treatment of HCV infection, including acute infection, may represent an important step in preventing subsequent infections. In addition to treating HCV infection, it is important to continue with education on risk-reduction approaches, such as harm-reduction programs and safer-sex strategies [37].

3.9 Subjects on Hemodialysis

The prevalence rate of HCV infection is markedly elevated in persons receiving hemodialysis, with a range of 2.6–22.9% in a large multinational study [38]. Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risk in persons on hemodialysis, and clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

HCV-infected persons receiving hemodialysis have a decreased quality of life, and increased mortality compared with uninfected persons on hemodialysis. In addition, HCV has a deleterious impact on kidney transplantation outcomes, with decreased patient and graft survival [39].

3.10 Patients with Acute Hepatitis or Recent Exposure

DAAs have been evaluated in several studies in patients with acute HCV infection, with reported SVR rates of almost 100%. In these patients, DAA-based regimens have been administered for a short duration (4–8 weeks) with excellent SVR rates [40, 41].

3.11 Patient Evaluation

In patients diagnosed with HCV infection, linking to medical care for further evaluation is important. This includes a complete history and physical examination, laboratory testing, and evaluation of fibrosis.

3.11.1 History and Physical Examination

The history should include relevant previous disease and questions regarding factors associated with accelerated disease progression (e.g., alcohol use, drug use, metabolic complications associated with fatty liver, and liver disease symptoms), complications that would suggest underlying cirrhosis (e.g., ascites, hematemesis,

and mental status changes), and factors that may affect the patient's candidacy for antiviral therapy.

The physical examination should include evaluation for stigmata of advanced liver disease such as spiders, palmar erythema, hepatomegaly, and splenomegaly, and signs of extrahepatic manifestations of HCV infection, such as vasculitis or cryoglobulinemia [1, 2].

3.11.2 Laboratory Testing

Blood tests should include a complete blood count, aminotransferase and alanine aminotransferase levels, measures of synthetic function, bilirubin, prothrombin time, albumin, renal function parameters, glucose, lipid panel, thyroid function tests, urinalysis, and a pregnancy test in women of childbearing potential.

Additionally, it is reasonable to evaluate for and exclude other causes of chronic liver disease, such as iron overload syndromes or autoimmune hepatitis, in patients with elevated aminotransferases. Because of the association between HCV and certain types of renal disease (e.g., mixed cryoglobulinemia and membranoproliferative glomerulonephritis), HCV-infected patients should be screened for proteinuria, hematuria, hypertension, and renal function.

3.12 HCV and Other Virological Markers

Assessment of HCV infection includes viral load (quantitative HCV RNA) and HCV genotype and subtype. Determination of HCV genotype, upon which the regimen, dosing, and duration of therapy as well as the likelihood of response depend, is essential to establish treatment decisions. HCV-infected patients should be tested for human immunodeficiency virus (HIV) and hepatitis B virus (HBV), given the common modes of transmission and the association of these coinfections with more rapid disease progression. Patients coinfected with HCV and HBV are at risk of HBV reactivation when DAAs are used and should be evaluated for HBV prophylaxis [1, 2, 42].

3.13 Assessment of Liver Disease

Liver disease evaluation includes the degree of fibrosis, particularly identification of advanced fibrosis or cirrhosis, important information for guiding treatment decisions (including duration) and surveillance. Although liver biopsy has been the gold standard in the diagnosis, this has been substituted by noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection.

Transient liver elastography is a noninvasive method to measure liver stiffness and correlates well with the measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. Elastography is one of the most widely used

tests for this purpose, with results of 12.5 Kpa being suggestive of liver cirrhosis [43, 44, 45]. If liver elastography is not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can also be very useful to exclude liver cirrhosis [45].

Assessment of host factors such as the history of prior antiviral treatment, identification of comorbidities associated with HCV infection, and concurrent medication use is also essential. Regarding comorbidities, these include extrahepatic manifestations of chronic HCV infection, such as cryoglobulinemia, HCV-associated renal disease, porphyria cutanea tarda, and autoimmune disorders. In patients taking concurrent medications, assessment of potential drug–drug interactions with selected antiviral drugs is recommended prior to the start of therapy, paying special attention to anticonvulsants, digoxin and amiodarone, rifamycin, statins, glucocorticoids, and antiretrovirals [46].

3.14 Counseling Patients

Diet and behavior. Patients should be informed about the natural history of HCV infection and counseled on potentially modifiable factors that are associated with accelerated liver disease, including alcohol use and obesity. Because of the association with more rapid progression of fibrosis, complete avoidance of alcohol and weight loss in obese patients should be recommended for HCV-infected individuals [1, 2].

3.15 Transmission Risk

Transmission of HCV is primarily through exposure to infected blood. Counseling should include discussions about the specific routes of HCV transmission and advice on measures to decrease the risk of transmission to other individuals. Women of childbearing age may also be concerned about the risk of perinatal transmission. Persons using injection drugs should be counseled on substance abuse treatment, including psychiatric services or opioid substitution therapy. Active injection drug use is not a contraindication for antiviral therapy, as long as the patient wishes to be treated and is willing and able to adhere to close monitoring during treatment.

3.16 Dose Adjustments of Medications

Certain medications, including over-the-counter agents, interact with various DAAs and may need to be adjusted during therapy [46].

Finally, untreated patients need life-long monitoring. Although the ideal interval for monitoring assessment has not been established, yearly evaluation is appropriate to discuss modifiable risk factors and to update testing for hepatic function and markers of disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum evaluation of every 6 months. In

resource-limited locations or other settings where HCV RNA testing is not accessible, HCV core antigen testing may be a more affordable alternative, if available.

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Available Agents: Contraindications and Potential Drug–Drug Interactions

4

Saye Khoo, Fiona Marra, and Alison Boyle

4.1 Introduction

The universal roll-out of direct-acting antiviral (DAA) agents has revolutionised the treatment of hepatitis C infection resulting in a treatment and cure option for nearly every individual who wants treatment. Those patients that still remain difficult to treat are often due to the management of complex drug interactions. As we move into an era of increased access to treatment, we widen the pool of healthcare providers who treat patients to include general practitioners, drug treatment teams, prison staff and pharmacists. The understanding of the role of drug interactions becomes even more important in making sure patients safely complete treatment successfully.

DAAs for the treatment of hepatitis C (HCV) include NS3 protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors. They work by inhibiting viral replication by targeting specific nonstructural proteins of the virus and results in disruption of viral replication and infection.

SVR rates of up to 99% in the well-tolerated and efficacious regimens currently licensed [1] means that the DAA pipeline has come to an end with the last two agents

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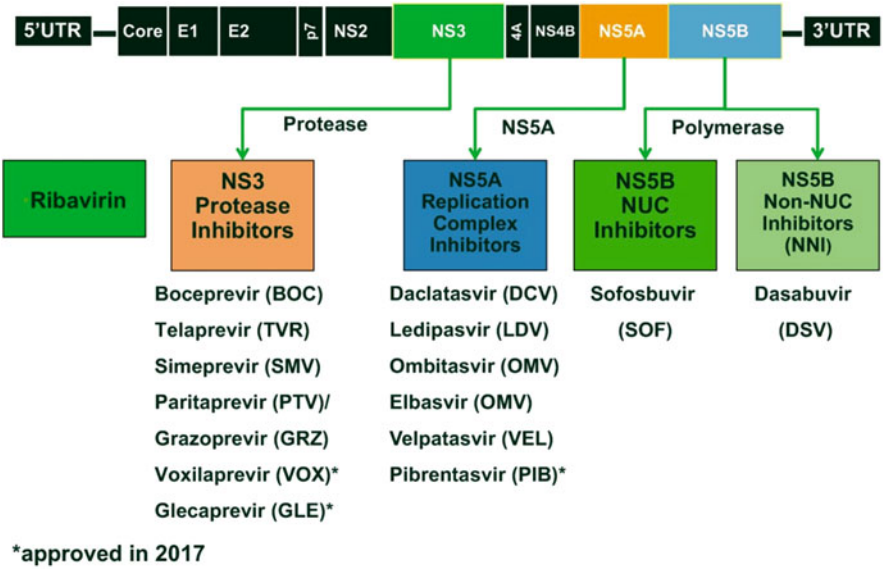

Fig. 4.1 FDA-approved DAAs

licensed in Europe in 2017. Three classes of DAAs are commonly combined to treat hepatitis C in either 2- or 3-drug regimens. These are listed in Fig. 4.1.

4.2 Mechanisms of Drug–Drug Interactions

All DAAs have the potential for clinically significant drug–drug interactions (DDIs). These are perhaps more relevant given the WHO eradication target for 2030 where larger numbers of patients now have access to HCV treatment around the globe. HCV-infected patients often take many co-medications to manage other co-morbidities.

Management of DDIs may include stopping or changing a co-medication, changing a dose, managing additional risk by establishing a monitoring plan (such as checking drug levels or taking additional bloods) or even recommending a different DAA. Most DAAs are metabolised in the liver by cytochrome P450 (CYP) enzymes or are both substrates and inhibitors of drug transporters [2]. This means DAAs can be victims or perpetrators of DDIs. As perpetrators, they cause increased or decreased exposure to concomitantly administered medications resulting in the possibility of toxic levels or suboptimal concentrations. As victims of DDIs, the DAAs themselves can be subject to drug interactions whereby the co-medication can increase the exposure of the DAA resulting in toxicity or reduce it resulting in subtherapeutic levels and potentially virological failure.

Taking a thorough drug history from the patient, often via different sources is crucial in providing the correct advice. This includes knowledge of over-the-counter preparations, contraceptives, herbal or vitamin supplements or illicit drug use. Accessing up-to-date sources to understand the clinical significance of drug interactions is important and a commonly used website from the University of Liverpool is www.hep-druginteractions.org. The mechanism of drug interactions for currently recommended DAAs are listed in Fig. 4.2.

DAA	VICTIM		PERPETRATOR			
	Metabolism (enzyme)	Transporter	Metabolism (enzyme)		Transporter	
			Inhibitor	Inducer	Inhibitor	Inducer
Sofosbuvir	-	BCRP, P-gp	-	-	-	-
Sofosbuvir + Ledipasvir		Sofosbuvir: BCRP, P-gp Ledipasvir: BCRP, P-gp	Ledipasvir: Intestinal CYP3A4, UGT1A1 (in vitro)	Ledipasvir: (weak) CYP3A4, CYP2C and UGT1A1	Ledipasvir: P-gp, BCRP	
Sofosbuvir + Velpatasvir	Velpatasvir: CYP2B6, CYP2C8 and CYP3A4	Sofosbuvir: BCRP, P-gp Velpatasvir: BCRP, P-gp, OATP1B1			Velpatasvir: P-gp, BCRP, OATP 1B1/B3	
Sofosbuvir, Velpatasvir, Voxilaprevir	Velpatasvir: CYP2B6, CYP2C8 and CYP3A4 Voxilaprevir: CYP3A4	Sofosbuvir: BCRP, P-gp Velpatasvir: BCRP, P-gp, OATP1B1/3 Voxilaprevir: BCRP, P-gp, OATP1B1/3			Velpatasvir: P-gp, BCRP, OATP1B1/3 Voxilaprevir: P-gp, BCRP, OATP 1B1/3	
Paritaprevir/r ,Ombitasvir + Dasabuvir	Paritaprevir: CYP3A4 Ritonavir: CYP3A4, 2D6 Dasabuvir: CYP2C8	Paritaprevir: OATP 1B1, BCRP, P-gp Dasabuvir: P-gp, BCRP, OCT1	Paritaprevir: UGT1A1 Ritonavir: CYP3A4, CYP2C8, CYP2D6 (?) Ombitasvir: UGT1A1 Dasabuvir: UGT1A1	Ritonavir: CYP1A2, CYP2C19	Paritaprevir: OATP 1B1/3, 2B1, BCRP, P-gp Ritonavir: OATP2B1, BCRP, OCT1, P-gp (in vitro) Dasabuvir: BCRP, P-gp	
Grazoprevir + Elbasvir	Grazoprevir: CYP3A4 Elbasvir:CYP 3A4	Grazoprevir: OATP1B1, P-gp, BCRP Elbasvir: P-gp	Grazoprevir: CYP3A4 (weak)		Grazoprevir: BCRP (intestinal) Elbasvir: BCRP, P-gp (Intestinal)	
Glecaprevir + Pibrentasvir	Glecaprevir: CYP3A4 Pibrentasvir: CYP3A4	Glecaprevir: BCRP, P-gp, OATP1B1/3 Pibrentasvir: BCRP, P-gp	Glecaprevir: CYP3A4 (weak), UGT1A1 Pibrentasvir: CYP3A4 (weak), UGT1A1		Glecaprevir: BCRP, P-gp, OATP1B1/3 Pibrentasvir: BCRP, P-gp, OATP1B1/3	

Fig. 4.2 Mechanisms of drug interactions

4.3 Pharmacology of individual Directly Acting Antivirals

4.3.1 Sofosbuvir

Sofosbuvir is dosed at 400 mg once a day, with or without food as a pan-genotypic NS5B. It undergoes renal excretion (80%) with 15% excreted in faeces. The active nucleoside metabolite GS-331007 is responsible for 78% of the sofosbuvir dose recovered in urine, while 3.5% is recovered as sofosbuvir [3].

Renal clearance, via active secretion, is the major elimination pathway for nucleoside metabolite GS-331007 (up to 20-fold), seen in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or with end-stage renal disease. Compared to patients with normal renal function (eGFR >80 mL/min/1.73 m^2), the sofosbuvir AUC was 61%, 107% and 171% higher in patients with mild, moderate and severe renal impairment, while the GS-331007 AUC was 55%, 88% and 451% higher, respectively. Despite this, no dose adjustment is required for patients with mild, moderate or severe renal impairment. The license was updated in 2020 to say that sofosbuvir can be used in these patients with no dose adjustment when no other relevant treatment options are available.

Sofosbuvir does not undergo cytochrome P450 metabolism but is transported by P-gp [4]. As a result, co-prescribing with an inducer may significantly decrease of sofosbuvir plasma concentrations that may lead to a suboptimal therapeutic effect. Thus, sofosbuvir should not be administered with drugs, such as rifampicin, carbamazepine, phenobarbital, phenytoin or St. John's wort. Other more moderate P-gp, interactions may occur with rifabutin, rifapentine and modafinil. There are no potential drug–drug interactions with any highly active antiretroviral treatment (HAART).

Sofosbuvir containing DAAs is not recommended in patients who are being treated with the anti-arrhythmic amiodarone due to the risk of life-threatening arrhythmias. Bradycardia has been observed from a range of hours to days after starting the DAA, but cases have been observed up to 2 weeks after initiating HCV treatment. The mechanism of interaction is still unclear, although a number of potential mechanisms have been proposed involving P-gp inhibition, protein binding displacement and direct effects of sofosbuvir and/or other DAAs on cardiomyocytes or ion channels [5]. It is possibly a combination of more than one mechanism. Amiodarone has a very long half-life and any interaction may persist for several months after discontinuation of amiodarone. In the absence of clear knowledge of the precise mechanism of this interaction, caution should be exercised with antiarrhythmics other than amiodarone [6].

4.3.2 Sofosbuvir and Ledipasvir

Sofosbuvir (NS5B inhibitor) and ledipasvir (NS5A inhibitor) are available in a single-tablet fixed-dose tablet containing 400 mg of sofosbuvir and 90 mg of ledipasvir. One tablet should be taken orally once daily with or without food [7].

Biliary excretion is the main route of elimination of unchanged ledipasvir with renal excretion being a minor pathway. The median terminal half-lives of sofosbuvir and GS-331007 of sofosbuvir/ledipasvir were 0.5 and 27 hours, respectively. Neither sofosbuvir nor ledipasvir are substrates for hepatic uptake transporters.

Ledipasvir is licensed in patients with decompensated cirrhosis (Childs Pugh B and C) as the area under the curve (AUC)—i.e. the plasma exposure is comparable in healthy volunteers and all degrees of hepatic impairment. Population analysis of pharmacokinetics in HCV-infected patients also indicated that decompensated cirrhosis had no clinically relevant effect on the exposure to ledipasvir [8].

Similar to sofosbuvir alone, no dose adjustment of sofosbuvir and ledipasvir is required for patients with mild, moderate or severe renal impairment.

Since the combination contains both ledipasvir and sofosbuvir, any interactions identified with the individual drugs will apply to the combination. The few interactions with sofosbuvir have been previously discussed. Since both ledipasvir is also transported by intestinal P-gp and BCRP, any co-administered drugs that are potent P-gp inducers will decrease not only sofosbuvir but also ledipasvir plasma concentrations, leading to a potentially suboptimal therapeutic effect. Co-administration with drugs that inhibit P-gp and/or BCRP may increase the exposure of sofosbuvir and ledipasvir, this is unlikely to be clinically significant. Ledipasvir may also cause drug interactions due to inhibition of P-gp and/or BCRP. Thus, caution is recommended with P-gp substrates such as digoxin and dabigatran, but also potentially with other drugs that are, in part, transported by these proteins (e.g. aliskiren, amlodipine, buprenorphine, carvedilol, cyclosporine) [6]. The use of rosuvastatin is also contraindicated (due to inhibition of hepatic OATP1B1 by ledipasvir) and interactions with certain other statins should be considered.

Ledipasvir solubility is pH-dependent and drugs that increase gastric pH such as antacids, H2-receptor antagonists and proton pump inhibitors will likely decrease concentrations of ledipasvir. H2-receptor antagonists can be given simultaneously or 12 hours apart at a dose not exceeding that equivalent to famotidine 40 mg and proton pump inhibitors simultaneously at a dose comparable to omeprazole 20 mg. Real-world data have suggested slightly reduced SVR rates in patients receiving high-dose proton pump inhibitors although conflicting data argue the significance of the interaction [9, 10].

Sofosbuvir/ledipasvir may be given with all antiretrovirals. However, due to an increase in tenofovir disoproxil fumarate (TDF) concentrations when a pharmacokinetic enhancer (ritonavir or cobicistat) is present in an antiretroviral regimen—in essence a double boosting effect on TDF as ledipasvir may increase TDF levels via P-gp inhibition. These combinations should be used with caution, with renal monitoring. Tenofovir levels are also increased in efavirenz-containing regimens and caution is required. Tenofovir alafenamide (TAF), which results in considerably lower plasma tenofovir levels, means that there is less concern about this interaction leading to increased tenofovir exposure [11].

4.3.3 Sofosbuvir and Velpatasvir

Sofosbuvir and velpatasvir are available in a single-tablet fixed-dose combination containing 400 mg of sofosbuvir and 100 mg of velpatasvir. Dosing is one tablet taken orally each daily with or without food.

Velpatasvir is metabolised in vitro by CYP2B6, CYP2C8 and CYP3A4. A slow turnover means that the vast majority in plasma is the parent drug. Biliary excretion is the major route of elimination of velpatasvir which is transported by P-gp, BCRP and, to a limited extent, OATP1B1. It has a median terminal half-life approximately of 15 hours.

The AUC of velpatasvir is similar in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function and is therefore recommended in all degrees of liver disease. Decompensated cirrhosis has no clinically relevant effect on velpatasvir exposure in a population pharmacokinetic analysis in HCV-infected subjects [12].

Drugs that are potent P-gp or potent CYP inducers (e.g. rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St John's wort) are contraindicated, due to the decrease in sofosbuvir and/or velpatasvir exposure with the potential loss in efficacy. However moderate P-gp or CYP inducers which can reduce velpatasvir exposure may also be clinically important.

Similar to ledipasvir, there is some concern about the inhibition of P-gp and/or BCRP by velpatasvir, such that there is an increase in exposure of a co-medication that is a substrate for these transporters [13]. Current thinking is that sofosbuvir/velpatasvir may be co-administered with P-gp, BCRP, OATP and CYP substrates, but there clearly needs to be some caution with co-medications that have a narrow therapeutic window and in which an increase in drug exposure could potentially have clinical consequences [6].

Like ledipasvir, the solubility of velpatasvir decreases as pH increases. Therefore, it is important to be aware of the recommendations concerning the co-administration of antacids, H2-receptor antagonists and proton pump inhibitors. For most patients, proton pump inhibitors should be avoided during sofosbuvir/velpatasvir treatment. If considered necessary, sofosbuvir/velpatasvir should be given with food and taken 4 hours before the proton pump inhibitor (at maximum dose comparable to omeprazole 20 mg).

In HIV–HCV co-infected patients, sofosbuvir/velpatasvir may be given with most antiretrovirals, the exceptions being the inducing drugs efavirenz, etravirine and nevirapine. Efavirenz causes a 50% decrease in velpatasvir exposure. Sofosbuvir/velpatasvir also increases tenofovir exposure due to P-gp inhibition [14]. This means that patients on a regimen containing tenofovir disoproxil fumarate will need to be monitored for renal adverse events.

4.3.4 Sofosbuvir, Velpatasvir and Voxilaprevir

Sofosbuvir, velpatasvir and voxilaprevir are available in a three-drug fixed-dose combination containing 400 mg of sofosbuvir, 100 mg of velpatasvir and 100 mg of voxilaprevir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with food as voxilaprevir plasma exposure (AUC) and maximum concentration (C_{max}) were 112–435% and 147–680% higher, respectively, in the presence of food [15].

The specific pharmacokinetic information related to sofosbuvir and velpatasvir individually is discussed in previous sections. Voxilaprevir is metabolised in vitro by CYP3A4 with the vast majority of drug in plasma being the parent drug. Velpatasvir and voxilaprevir are both inhibitors of drug transporters P-gp, BCRP, OATP1B1 and OATP1B3. Biliary excretion of the parent drug is the major route of elimination for voxilaprevir. The median terminal half-life of voxilaprevir following administration of sofosbuvir, velpatasvir and voxilaprevir is approximately 33 hours [16].

Population pharmacokinetic analysis of voxilaprevir in HCV-infected patients indicated that patients with compensated cirrhosis (Child–Pugh A) had 73% higher exposure of voxilaprevir than those without cirrhosis. Thus, no dose adjustment of sofosbuvir, velpatasvir and voxilaprevir is required for patients with compensated cirrhosis. The pharmacokinetics of single-dose voxilaprevir was also studied in patients with moderate and severe hepatic impairment (Child–Pugh Class B and C, respectively). Relative to patients with normal hepatic function, the voxilaprevir AUC was threefold and fivefold higher in patients with moderate and severe hepatic impairment, respectively. The combination of sofosbuvir, velpatasvir and voxilaprevir is therefore not recommended in patients with moderate hepatic impairment (Child–Pugh B) and contraindicated in those with severe hepatic impairment (Child–Pugh C).

Because velpatasvir and voxilaprevir are both inhibitors of P-gp, BCRP, OATP1B1 and OATP1B3, co-administration of sofosbuvir, velpatasvir and voxilaprevir with medicinal products that are substrates of these transporters may increase the exposure of the co-medications. This means that those for which elevated plasma levels are associated with serious events are contraindicated and others may require dose adjustment or additional monitoring. Rosuvastatin is contraindicated due to a 19-fold increase in plasma exposure of the statin. As this effect is likely to be attributed more to the BCRP transporter, other drugs that are a BCRP substrate, including methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, sulfasalazine and topotecan, are also not recommended [6]. Dabigatran is contraindicated due to a nearly threefold increase in AUC. This is caused by P-gp inhibition by both velpatasvir and voxilaprevir. Other substrates of P-gp may need to be dose-adjusted or monitored for increased exposure, including digoxin, ticagrelor, carvedilol, diltiazem and aliskiren. Similar caution is required with OATP1B inhibitors such as ciclosporin as voxilaprevir plasma exposure increases 19-fold, or with OATP1B substrates such as edoxaban as voxilaprevir inhibition is expected to increase the exposure of the factor Xa inhibitor. These combinations are both not recommended.

Concomitant use with medicinal products that are strong P-gp and/or strong CYP inducers such as rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital or phenytoin are contraindicated due to the decrease in sofosbuvir, velpatasvir and/or voxilaprevir exposure with the potential loss in efficacy [16]. However, there are also drugs that are moderate P-gp or CYP inducers (such as modafinil, efavirenz, oxcarbazepine and others) which can also reduce exposure of this DAA, and currently these are also not recommended.

For women of childbearing age, concomitant use with ethinylestradiol-containing contraception is contraindicated due to the risk of ALT elevations. Progestogen-containing contraception is allowed.

The solubility of velpatasvir decreases as pH increases. Therefore, it is important to be aware of the recommendations concerning the co-administration of antacids, H2-receptor antagonists and proton pump inhibitors. Proton pump inhibitors can be given with sofosbuvir/velpatasvir/voxilaprevir at a dose that does not exceed doses comparable with omeprazole 20 mg. Sofosbuvir/velpatasvir/voxilaprevir should be given with food and taken 4 hours before the proton pump inhibitor if possible.

In HIV–HCV co-infected patients, sofosbuvir/velpatasvir/voxilaprevir is not recommended with the inducing drugs efavirenz, etravirine and nevirapine, and the protease inhibitors atazanavir/ritonavir and lopinavir/ritonavir. Caution is required with twice-daily darunavir/ritonavir, darunavir/cobicistat and atazanavir/cobicistat as there are no data. Efavirenz causes a 50% decrease in velpatasvir exposure and atazanavir causes a fourfold increase in voxilaprevir exposure. Sofosbuvir/velpatasvir/voxilaprevir also increases tenofovir exposure due to P-gp inhibition [17]. This means that patients on a regimen containing TDF need to be monitored for renal adverse events.

4.3.5 Paritaprevir (+ritonavir), Ombitasvir and Dasabuvir

Paritaprevir is an NS3-4A protease inhibitor that is metabolised primarily by CYP3A4 and is given with a low dose of the CYP3A inhibitor ritonavir as a pharmacokinetic enhancer. Ritonavir is not active in the treatment of HCV. Its use enables once-daily administration and a lower dose than would be required without ritonavir. Ombitasvir is an NS5A inhibitor given in a fixed-dose combination with paritaprevir/ritonavir. The recommended dose of this combination is two tablets of ritonavir/paritaprevir/ombitasvir (50 mg/75 mg/12.5 mg per tablet) taken orally once daily with food. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase in 250 mg tablets administered twice daily in combination with ritonavir/paritaprevir/ombitasvir in genotype 1 patients.

Paritaprevir is excreted predominantly into the faeces. Ombitasvir shows linear kinetics and is predominantly eliminated in the faeces. Dasabuvir is metabolised in the liver, and its predominant metabolite is mainly cleared via biliary excretion and faecal elimination with minimal renal clearance [18].

Paritaprevir with ritonavir and ombitasvir with or without dasabuvir is not recommended for patients with Child–Pugh B and is contraindicated in patients

with Child–Pugh C liver disease as the AUC of paritaprevir increased 9.5-fold in Child–Pugh C. In Child–Pugh B, there is an increase in paritaprevir exposure of 62%. No dose adjustment is required for patients with mild hepatic impairment (Child–Pugh A).

No dose adjustment is required for patients with mild, moderate or severe renal impairment. Paritaprevir, ombitasvir and dasabuvir can also be prescribed to patients on haemodialysis. The AUC of paritaprevir was increased 45% in patients with severe renal impairment (creatinine clearance 15–29 mL/min).

Paritaprevir is primarily metabolised by CYP3A4, dasabuvir is primarily metabolised by CYP2C8 and ombitasvir undergoes hydrolysis. Ombitasvir and dasabuvir can be metabolised by CYP3A4. Transporters interactions are also significant with paritaprevir inhibiting OATP1B1/B3, P-gp and BCRP. Dasabuvir and ritonavir may also inhibit P-gp and BCRP [19].

As a potent inhibitor of CYP3A4, ritonavir is the perpetrator of many significant drug interactions. A number of drugs are contraindicated because elevated plasma exposure would lead to serious adverse events, including but not exclusive to: alfuzosin, amiodarone, lovastatin, simvastatin, atorvastatin, oral midazolam, quetiapine, quinidine, salmeterol, sildenafil when used for pulmonary arterial hypertension [6]. Also contraindicated are enzyme inducers that may result in suboptimal efficacy (e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort, enzalutamide) and enzyme inhibitors that might increase paritaprevir exposure (e.g. azole antifungals, clarithromycin [20, 21]).

There are many restrictions with HIV co-infection and expert pharmacist advice should be sought. Atazanavir and darunavir should be taken without ritonavir and all other protease inhibitors are contraindicated. Efavirenz, etravirine and nevirapine are contraindicated, and rilpivirine should be used cautiously with ECG monitoring. Cobicistat-containing regimens should not be used due to an additive boosting effect [22].

4.4 Grazoprevir and Elbasvir

Grazoprevir and elbasvir are prescribed in a single-tablet combination containing 100 mg of grazoprevir and 50 mg of elbasvir dosed at one tablet daily with or without food.

Grazoprevir and elbasvir are partially metabolised by CYP3A4 with biliary and faecal elimination and $<1\%$ recovered in urine. Grazoprevir is transported by P-gp and OATP1B1, while elbasvir is a substrate for P-gp. The terminal half-life values are approximately 24 and 31 hours, respectively.

No dose adjustment is required in Child–Pugh A cirrhosis as Grazoprevir exposure is increased by 70%. It is contraindicated in patients with moderate (Child–Pugh B) or severe (Child–Pugh C) hepatic impairment due to fivefold and 12-fold increases in AUC respectively. No dose adjustment is required in patients with mild, moderate or severe renal impairment (including patients on haemodialysis or peritoneal dialysis) [23].

Inducers of efavirenz, etravirine, phenytoin, carbamazepine, bosentan, modafinil and St. John's wort may cause a significant decrease in plasma exposure of both DAAs and are contraindicated as elbasvir and grazoprevir are substrates of CYP3A and P-gp. Strong inhibitors of CYP3A (e.g. boosted protease inhibitors, some azole antifungals), which may markedly increase plasma concentrations, are either contraindicated or not recommended. Grazoprevir plasma concentrations may also be significantly increased by inhibitors of OATP1B1 (including boosted protease inhibitors, cobicistat, cyclosporin, single-dose rifampicin). There is no effect of acid-reducing agents on the absorption of either DAA.

The potential for grazoprevir/elbasvir to affect other medications is relatively low, although grazoprevir is a weak CYP3A inhibitor (approximately 30% increase in midazolam exposure) and elbasvir a weak inhibitor of P-gp. Narrow therapeutic index drugs should be co-prescribed with caution (e.g. tacrolimus, some statins, dabigatran, ticagrelor), or drugs with large ranges such a quetiapine where those on higher doses may need additional monitoring, dose reduction and/or ECG.

In patients with HIV co-infection, there are cautions on which antiretrovirals can be co-administered with elbasvir/grazoprevir including NNRTIs and protease inhibitors [24–26].

4.5 Glecaprevir and Pibrentasvir

Glecaprevir and pibrentasvir are available in a fixed-dose combination containing 100 mg of glecaprevir and 40 mg of pibrentasvir. Three tablets should be taken orally a day with food as glecaprevir plasma exposure increases 83–163% in the presence of food compared to the fasted state. They are eliminated via biliary excretion and have a terminal half-life of approximately 6 and 23 hours, respectively [27].

Glecaprevir and pibrentasvir can be prescribed in patients with Child–Pugh A cirrhosis as population pharmacokinetic analysis in HCV-infected subjects showed with compensated (Child–Pugh A) cirrhosis, exposure of glecaprevir was approximately twofold higher while pibrentasvir exposure was similar to non-cirrhotics. Glecaprevir/pibrentasvir is not recommended in patients with Child–Pugh B cirrhosis and contraindicated in those with Child–Pugh C cirrhosis [28] as when compared to patients with normal hepatic function, glecaprevir AUC was 100% higher in those with moderate hepatic impairment and increased to 11-fold in those with severe hepatic impairment.

Glecaprevir/pibrentasvir was studied in HCV-negative subjects with mild, moderate, severe or end-stage renal impairment not on dialysis compared to subjects with normal renal function. The AUCs were increased by less than 56% in all was not clinically significant. Glecaprevir/pibrentasvir AUC was also similar with and without dialysis.

Glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP and OATP1B1 and OATP1B3. Co-administration with glecaprevir/pibrentasvir may increase the concentration of co-medications that are substrates of P-gp (e.g. dabigatran etexilate

which is contraindicated due to a 2.4-fold increase in dabigatran exposure), BCRP (e.g. rosuvastatin which requires a dose reduction) or OATP1B1/3 (e.g. atorvastatin or simvastatin which are contraindicated). For other P-gp, BCRP, or OATP1B1/3 substrates, dose adjustment should be considered [29].

Glecaprevir/pibrentasvir administered with strong P-gp and CYP3A inducing drugs such as rifampicin, carbamazepine, St. John's wort or phenytoin may result in suboptimal drug concentrations, risking virological failure. Co-administration with these, or other potent inducers, is contraindicated. A similar effect should be considered with moderate inducers such as oxcarbazepine and eslicarbazepine. Co-medications that inhibit OATP1B1/3 such as ciclosporin, darunavir and lopinavir and P-gp and BCRP inhibitors may increase glecaprevir concentrations [30].

The potential for glecaprevir/pibrentasvir to affect other medications is relatively low, although glecaprevir is a weak CYP3A inhibitor (approximately 27% increase in midazolam exposure). Caution is required when co-administering drugs metabolised via CYP3A4 of a narrow therapeutic index or drugs with large ranges such as quetiapine, where patients on higher doses may need additional monitoring, dose reduction and/or ECG.

For women of childbearing age, concomitant use with ethinylestradiol-containing contraception is contraindicated due to the risk of ALT elevations. Progestogen-containing contraception is recommended [6].

Similar to other DAAs, the solubility of glecaprevir decreases as pH increases; however, no dose adjustment is required. There is minimal data with doses equivalent to higher than omeprazole 40 mg, so caution should be exercised with these high doses (C_{max} of glecaprevir decreases on average by 64% when co-administered with omeprazole 40 mg).

In patients co-infected with HIV, glecaprevir/pibrentasvir is contraindicated with atazanavir-containing regimens and is not recommended with other HIV protease inhibitors. Similarly, the inducing NNRTIs efavirenz, etravirine and nevirapine are not recommended due to an expected reduction in plasma exposure of glecaprevir/pibrentasvir [30].

4.6 DDI Advice for Specific Therapeutic Areas

A summary of DDIs between HCV DAAs and a variety of co-medications can be accessed from www.hep-druginteractions.org. The following section discusses the management of complex DDIs with HCV DAAs in specific therapeutic areas.

4.6.1 Antiretrovirals (ARVs)

The excellent cure rates observed with modern HCV regimens confirms that HIV–HCV co-infected patients should no longer be regarded as a 'special' population at risk of suboptimal responses—nevertheless, additional considerations should be

Table 4.1 Drug–drug interactions between HCV DAAs and HIV antiretrovirals

		SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLE/PIB
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆	◆
	Tenofovir disoproxil fumarate (TDF)	◆	■	■	◆	◆	◆	■	◆
	Tenofovir alafenamide (TAF)	◆	◆	◆	■	◆	◆	■	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●	●
	Etravirine	◆	◆	●	●	●	■	●	●
	Nevirapine	◆	◆	●	●	●	■	●	●
	Rilpivirine	◆	◆	◆	■	◆	◆	◆	◆
Protease	Atazanavir/ritonavir	◆	◆*	◆*	■	●	■	●	●
	Atazanavir/cobicistat	◆	◆*	◆*	●	●	■	●	●
	Darunavir/ritonavir	◆	◆*	◆*	■	●	◆	■*	●
	Darunavir/cobicistat	◆	◆*	◆*	●	●	■	◆*	●
	Lopinavir/ritonavir	◆	◆*	◆*	●	●	◆	●	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (TDF)	◆	■*	■*	●	●	■	■*	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF)	◆	◆	◆	●	●	■	◆	◆
	Maraviroc	◆	◆	◆	■	◆	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆	◆

Colour Legend

◆ No clinically significant interaction expected.

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

* Known or anticipated increase in tenofovir concentrations in regimens containing tenofovir disoproxil fumarate. Caution and frequent renal monitoring.

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r + DSV* ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *DCV* daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

borne in mind when treating this population. These centre around the increased propensity for significant DDIs impacting upon HIV and/or HCV therapy. For most patients, DDIs associated with lifelong HIV therapy given together with comparatively short-course HCV are surmountable, particularly for the prize of complete HCV eradication.

A summary of HIV–HCV DDIs is presented in Table 4.1. Individual HIV and HCV drug regimens should be searched online for the most current treatment advice, but for the purposes of this brief review, they can be grouped according to mechanisms as follows.

4.6.2 DDIs Involving HCV NS3-4A Protease Inhibitors and HIV Drugs Which Inhibit or Induce Their Clearance

Although individual differences exist, the NS3-4A protease inhibitors paritaprevir, grazoprevir, glecaprevir and voxilaprevir are substrates of cytochrome P450 CYP3A or certain drug transporters, and are thus, as a class, susceptible to DDIs with potent inhibitory (e.g. HIV boosted PIs or cobicistat) or inducing (such as the NNRTIs efavirenz, etravirine, nevirapine) potential. The magnitude of the PK effect varies, as does the clinical tolerance of different regimens for changes in drug exposure that result. For example, HIV boosted PIs and cobicistat increase grazoprevir significantly (5.4–10.5-fold) and are contraindicated, as is co-administration with efavirenz/etravirine/nevirapine which can be expected to lower grazoprevir (and elbasvir) exposure through enzyme induction. Similarly, HIV PIs boosted with ritonavir increase glecaprevir concentrations by 4.4–8-fold, and NNRTIs (efavirenz/etravirine/nevirapine) reduce glecaprevir exposures and co-administration is not recommended. However, boosting with cobicistat has less of an impact with glecaprevir (~threefold increase) and co-administration with cobicistat (in the context of a fixed-dose integrase containing regimen, and in the absence of HIV PIs) is permissible.

Paritaprevir-containing regimens inherently incorporate ritonavir, which complicates the use of any HIV boosted PI regimen. In the case of atazanavir, the DAA regimen is used to boost atazanavir without any additional ritonavir. In the case of darunavir, a similar strategy is possible, although associated with a modest (50%) decrease in Ctrough of darunavir (in contrast to the USA prescribing information, the European SPC advises that once-daily darunavir can be used in the absence of extensive HIV PI resistance). Clearly, both the HIV PI and ritonavir-containing DAA regimen should be simultaneously ingested. Co-administration with cobicistat or the NNRTIs efavirenz/etravirine/nevirpine is contraindicated.

Voxilaprevir is a substrate of the transporters OATP1B1 and P-gp. Potent transporter inhibition by atazanavir plus ritonavir resulted in fourfold increases in voxilaprevir exposure, with similar increases expected with boosted lopinavir, and the combinations are contraindicated. However, darunavir given once-daily (boosted with ritonavir or cobicistat) is not expected to result in clinically significant DDIs (data for twice-daily darunavir are lacking). Conversely, co-administration with efavirenz resulted in a halving of velpatasvir exposure, and co-administration with efavirenz, etravirine or nevirapine is not recommended.

4.6.3 Interactions Involving Tenofovir Diproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF)

The active moiety tenofovir (TFV) is poorly bioavailable and thus administered as salts that cross the gut and are biotransformed to TFV (as is the case with TDF) or else remain as TAF until intracellular conversion to TFV. TAF is given at roughly a tenth of the dose of TDF (which may explain the lower rates of nephrotoxicity

observed), yet achieves around four times higher concentrations of tenofovir-diphosphate intracellularly. Other differences exist, for example with regard to transporters such as P-gp.

When co-administered with sofosbuvir/velpatasvir/voxilaprevir, TFV exposure increased by ~40% with TDF (probably through P-gp inhibition), and by 67–79% with TAF (although absolute plasma exposures of TFV are lower with TAF than with TDF). When given with ledipasvir (plus sofosbuvir), TFV exposure increased by ~98% (Cmin by 163%) with TDF, whereas no clinically significant changes were observed with TAF. The lower plasma TFV exposures observed following TAF dosing suggest that TAF may be safely co-administered with sofosbuvir/velpatasvir/voxilaprevir or with sofosbuvir/ledipasvir; however, increased renal monitoring is advised when dosing TDF with either DAA regimen, especially if TDF is given in the context of a boosted PI-containing regimen (where TFV exposures are already elevated). In Europe, TAF plus emtricitabine is available in a lower strength (10 mg TAF content) formulation, and this formulation is preferred to conventional dosing with 25 mg TAF, when given with OBV/PTV/r and DSV (containing ritonavir).

4.6.4 Miscellaneous DDIs Involving DAAs and Antiretrovirals

These include DDIs based around inhibition or induction of clearance. For example, daclatasvir is a substrate of CYP3A4 and P-gp, and also inhibits the transporters P-gp and OATB1B1. Thus, moderate interactions are likely with boosted PIs and with the NNRTIs efavirenz/etravirine/nevirapine. Some HIV drugs are sensitive to inhibition of hepatic cytochromes by paritaprevir/ritonavir/ombitasvir; these include maraviroc, any coformulation containing cobicistat, and also rilpivirine (where increased plasma concentrations from any drug interaction may increase the risk of QT prolongation).

In summary, although there may be significant DDIs between individual antiviral agents used for treating HIV and hepatitis C, there are now sufficient choices for both diseases to select alternative regimens that avoid these interactions while maintaining efficacy for both treatments. The prevalence of antiviral resistance for both diseases is set to decrease with the introduction of better drugs, but patients with multidrug resistance in either disease may still have limited choice. Management of therapy in this complex group of patients is best undertaken by prescribers with experience in both diseases. Importantly, harms are best prevented through complete and regular medicines reconciliation, and recognition of DDIs where they exist.

4.6.5 Proton Pump Inhibitors (PPIs)

Certain components of directly acting agents appear to exert pH-dependent solubility (Table 4.2). This effect was first described with NS5A inhibitor ledipasvir where the solubility of ledipasvir decreases as pH increases. Medicinal products such as proton pump inhibitors that increase gastric pH will decrease the concentration of

Table 4.2 Drug–drug interactions between HCV DAAs and PPIs

	SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLP/PIB
Esomeprazole	◆	■	■	■	◆	◆	■	■
Lansoprazole	◆	■	■	■	◆	◆	■	■
Omeprazole	◆	■	■	■	◆	◆	■	■
Pantoprazole	◆	■	■	■	◆	◆	■	■
Rabeprazole	◆	■	■	■	◆	◆	■	■

Colour Legend

◆ No clinically significant interaction expected.
■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r + DSV* ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, DCV daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

ledipasvir. Omeprazole 20 mg was dosed simultaneously with sofosbuvir/ledipasvir and ledipasvir Cmax decreased by 11% (up to 39% in individual patients) and AUC by 4%. The product license, therefore, states that proton pump inhibitor doses comparable to omeprazole 20 mg can be administered simultaneously with sofosbuvir/ledipasvir. Proton pump inhibitors should not be taken before sofosbuvir/ledipasvir. This effect has been extensively studied showing conflicting data on whether it affects SVR, although specific dosage and timing of administration was not always clear [31–36]. One study [32] showed a significantly decreased achievement of SVR among PPI users daily. Another showed that twice-daily PPI use was associated with incidence for SVR but not daily PPI use [33].

Velpatasvir, as part of sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir also exerts pH-dependent solubility. Omeprazole 20 mg dosed simultaneously with sofosbuvir/velpatasvir reduced velpatasvir Cmax by 37% and AUC by 36%. Separating the dose by 4 hours results in Cmax decrease of velpatasvir concentrations by 33% and AUC by 26%. As such, co-administration with proton pump inhibitors is not recommended in the product license. If it is considered essential to co-administer, then sofosbuvir/velpatasvir should be administered with food and taken 4 hours before proton pump inhibitor at maximum doses comparable to omeprazole 20 mg.

Not all NS5A inhibitors are affected in this way. Elbasvir [37] and ombitasvir [38] concentrations are not reduced by PPIs. Glecaprevir/pibrentasvir appears to exert pH-dependent solubility; however, in this instance, it is the NS3 inhibitor glecaprevir that is affected and not the NS5A inhibitor pibrentasvir. At a dose of omeprazole 20 mg, glecaprevir Cmax decreases by 22% and AUC 29%, at an

increased dose of omeprazole 40mg glecaprevir Cmax and AUC decreases by 64% and 49%, respectively. Efficacy data from clinical studies show that this did not impact SVR and no dose adjustment is recommended. There is no data for doses higher than omeprazole 40 mg.

In all incidences where PPIs may result in reduced concentrations of DAAs, a full drug history should be taken for appropriateness of prescribing in the first instance, and the proton pump inhibitor stopped if not necessary. H_2 antagonists can be considered as a step-down mechanism if patients are struggling to manage clinically without a PPI. Rafting agents could also be considered, separated if possible from the administration of DAA.

4.6.6 Anti-epileptic Drugs (AEDs)

AEDs are often associated with drug interactions with the older generation being particularly problematic (Table 4.3). Phenytoin, phenobarbital and carbamazepine

Table 4.3 Drug–drug interactions between HCV DAAs and AEDs

	SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLP/PIB
Carbamazepine	●	●	●	●	●	●	●	●
Clonazepam	◆	◆	◆	■	◆	◆	◆	◆
Ethosuximide	◆	◆	◆	■	◆	◆	◆	◆
Gabapentin	◆	◆	◆	◆	◆	◆	◆	◆
Lacosamide	◆	◆	◆	■	◆	◆	◆	◆
Lamotrigine	◆	◆	◆	■	◆	◆	◆	◆
Levetiracetam	◆	◆	◆	◆	◆	◆	◆	◆
Lorazepam	◆	◆	◆	■	◆	◆	◆	◆
Oxcarbazepine	●	●	●	●	●	●	●	●
Phenobarbital	●	●	●	●	●	●	●	●
Phenytoin	●	●	●	●	●	●	●	●
Topiramate	◆	◆	◆	◆	◆	◆	◆	◆
Valproate	◆	◆	◆	■	◆	◆	◆	◆

Colour Legend

◆ No clinically significant interaction expected.

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r + DSV* ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *DCV* daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

are strong CYP enzyme and p-glycoprotein inducers and are contraindicated with all DAAs. A change to an alternative (non-interacting) anti-epileptic should be considered to avoid subtherapeutic plasma levels of DAAs and risk of treatment failure.

Co-administration of AEDs and DAAs have not been frequently studied. The effect of co-administration of carbamazepine (200 mg twice daily) and OBV/PTV/r and DSV was reported in 12 subjects. Ombitasvir Cmax and AUC both decreased by 31%. Paritaprevir Cmax and AUC decreased by 66% and 70%. Ritonavir Cmax and AUC decreased by 83% and 87%. Dasabuvir Cmax and AUC decreased by 55% and 70%. Carbamazepine is a CYP enzyme substrate and therefore can also be affected by OBV/PTV/r and DSV enzyme inhibition/induction. Carbamazepine Cmax, AUC and Cmin were increased by 10%, 17% and 35%, respectively, with the Cmax, AUC and Cmin of the metabolite carbamazepine-10,11-epoxide decreasing by 16%, 25% and 43%, respectively [21, 22]. Co-administration of carbamazepine (200 mg twice daily) and glecaprevir/pibrentasvir decreased glecaprevir Cmax and AUC by 67% and 66%; pibrentasvir Cmax and AUC decreased by 50% and 51%. [30]. Both of these pharmacokinetic studies demonstrate a significant reduction in DAA plasma concentrations which may lead to a reduction in efficacy and loss of virological response.

Induction of hepatic enzymes appears to occur to a lesser extent with the newer AED oxcarbazepine. When compared with carbamazepine, the reduction of bioavailability of felodipine and ciclosporin (CYP3A4 substrates) was still present when co-administered with oxcarbazepine although the effect was less marked [39, 40]. Additionally, a 47% decrease in bioavailability of both ethinylestradiol and levonorgestrel was observed during treatment with oxcarbazepine in 16 healthy volunteers [41]. The authors concluded that this was likely to be, at least in part, explained by CYP3A4 enzyme induction. Taking this evidence into account, it would suggest that oxcarbazepine may have a mild to moderate inducing effect on CYP3A4 enzymes. As such, it should not be co-administrated with DAAs in the absence of further data. There is a published case report using an increased dose of daclatasvir in combination with oxcarbazepine. Oxcarbazepine was given with daclatasvir 90 mg once daily (as well as sofosbuvir and ribavirin) based on previous data with efavirenz (a moderate CYP3A4 inducer) [42, 43]. Although SVR12 was achieved in this patient, there remained a reduction in DAA exposure despite the increased doses given. These findings may be applicable in selected patients using this specific DAA regimen. However, this strategy cannot currently be extrapolated to all DAAs without further drug interaction studies. Additionally, as most DAAs are now available as fixed-dose combinations, increasing doses is difficult from a practical point of view as well as having potential financial implications.

The presence of ritonavir in OBV/PTV/r and DSV regimen leads to potential interactions with many AEDs, and may cause increased exposure (and subsequent risk of toxicity) via CYP enzyme inhibition or reduced exposure (and subsequent risk of treatment failure and seizure occurrence) via induction of glucuronidation (see Table 4.1). Caution is required for many AED drugs if used in combination with OBV/PTV/r and DSV. For example, valproate is metabolised via multiple UGTs, and induction of glucuronidation by ritonavir may result in a decrease in valproate

levels. Although OBV/PTV and DSV are all known to inhibit UGT1A1, this UGT demonstrated no activity for valproate glucuronidation [44]. Thus, OBV/PTV and DSV are unlikely to impact on valproate metabolism and any drug interaction will be due to the presence of ritonavir. If co-administration is deemed necessary, no a priori dose adjustment is advised but therapeutic drug monitoring of valproate levels is recommended [45]. Clonazepam, ethosuximide, lacosamide and lorazepam are CYP3A4 substrates, and exposure of these AEDs is predicted to increase in combination with OBV/PTV/r and DSV [41].

4.6.7 Immunosuppressants

Significant and complex drug–drug interactions can occur with DAAs and immunosuppressant drugs, particularly calcineurin inhibitors (CNIs), ciclosporin and tacrolimus and a related drug, sirolimus. Ciclosporin, tacrolimus and sirolimus are all substrates of CYP3A and P-gp [46–48]. (Table 4.4) Additionally, ciclosporin is a weak inhibitor of CYP3A as well as inhibiting several transporter proteins, including organic anion transporting polypeptide (OATP) 1B1, OATP1B3, BCRP and P-gp [49]. Although tacrolimus and sirolimus have demonstrated potential for CYP3A/P-gp inhibitory potential in vitro, they have been shown not to influence CYP3A/P-gp activity in vivo and therefore would be unlikely to affect exposure to drugs

Table 4.4 Drug–drug interactions between HCV DAAs and immunosuppressants

	SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLP/PIB
Azathioprine	◆	◆	◆	◆	◆	◆	◆	◆
Basiliximab	◆	◆	◆	◆	◆	◆	◆	◆
Ciclosporin (cyclosporine)	◆	◆	◆	■	●	◆	●	■
Etanercept	◆	◆	◆	◆	◆	◆	◆	◆
Mycophenolate	◆	◆	◆	■	◆	◆	◆	◆
Sirolimus	◆	◆	◆	●	■	◆	■	■
Tacrolimus	◆	◆	◆	●	■	◆	■	■

Colour Legend

◆ No clinically significant interaction expected.

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r* + DSV ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *DCV* daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

dependent on these pathways [50]. Similarly, tacrolimus has been shown to inhibit OATP in vitro but, as described with CYP3A and P-gp, various studies have shown that it does not cause OATP-mediated DDIs at therapeutic concentrations [51–53].

Tacrolimus exposure is slightly increased with co-administration of elbasvir/grazoprevir and glecaprevir/pibrentasvir and therapeutic drug monitoring (TDM) of tacrolimus blood levels to guide dose adjustments is recommended. Sirolimus has not been studied with these two DAAs but a similar interaction is anticipated and TDM recommended [41].

Sofosbuvir/velpatasvir/voxilaprevir has not been studied with either tacrolimus or sirolimus but may potentially increase levels due to p-gp inhibition. The clinical significance of this theoretical interaction is unclear and TDM would be prudent [41].

The interaction with OBV/PTV/r and DSV and CNIs is much more pronounced as there are multiple overlapping metabolic and transporter profiles between these therapies. Co-administration with OBV/PTV/r and DSV at steady state increased tacrolimus Cmax, Cmin and AUC by fourfold, 17-fold and 57-fold, respectively, and ciclosporin Cmin and AUC by 16-fold and 5.8-fold, respectively. Ciclosporin Cmax was not affected [54]. The pharmacokinetic parameters of OBV/ritonavir/DSV were only slightly affected ($\leq$ 34% change) by ciclosporin and tacrolimus, whereas PTV exposure was increased by ciclosporin (Cmax 44% and AUC 72% higher) and decreased by tacrolimus (Cmax 34% and AUC 43% lower). The safety and efficacy of the DAA regimen are not likely to be affected by these changes [50].

Sirolimus exposure is also affected by co-administration with OBV/PTV/r and DSV with Cmax, Cmin and AUC increasing by 6.4-fold, 19.6-fold and 38-fold, respectively, with no significant effect on DAA drug pharmacokinetics [21, 22].

The US product label for both tacrolimus and sirolimus states co-administration is contraindicated due to the potential for serious or life-threatening adverse effects; whereas, the European SPC for OBV/PTV/r and DSV recommends avoiding co-administration unless benefits outweigh the risks [(21, 22, 55)]. In patients for whom co-administration is deemed necessary, it is advised that initial immunosuppressant dose reduction occurs. Patients should reduce their total daily ciclosporin dose to one-fifth and take this dose once daily. Similarly, tacrolimus doses should be reduced to 0.5 mg every 7 days, and sirolimus reduced to 0.2 mg twice weekly [21, 22]. Frequent blood concentration monitoring is necessary with dose adjustment where indicated. This intensive monitoring should be continued once OBV/PTV/r and DSV treatment is completed until an immunosuppressant dose is stabilised.

Analysis of pharmacokinetic data from CORAL-I, a phase II study evaluating the safety and efficacy of OBV/PTV/r and DSV in post-transplant patients with chronic HCV, confirmed the validity of the recommended dosing strategies (for ciclosporin and tacrolimus) in maintaining therapeutic immunosuppression levels during treatment with this DAA regimen [56]. However, with the availability of other, non-interacting DAA regimens, it would seem prudent to avoid co-administration with OBV/PTV/r and DSV wherever possible.

As a potent OATP1B inhibitor, ciclosporin can also be the perpetrator of DDIs with DAAs. It is contraindicated with grazoprevir/elbasvir and sofosbuvir/velpatasvir/voxilaprevir. Co-administration of ciclosporin has been shown to increase exposure of grazoprevir by 15-fold and voxilaprevir by 9.4-fold. The safety of increases of this magnitude is not known although may lead to significant elevations in transaminases [16, 57]. Similarly, glecaprevir/pibrentasvir exposure was increased by fivefold when co-administered with ciclosporin 400 mg/day [34]. However, a lower dose of ciclosporin (100 mg/day) only slightly increased glecaprevir Cmax and AUC (by 30% and 37%, respectively) [58]. Subsequently, glecaprevir/pibrentasvir is not recommended for use in patients taking >100 mg/day ciclosporin [34].

4.6.8 Antiplatelets and Anticoagulants (Table 4.5)

Table 4.5 Drug–drug interactions between HCV DAAs and antiplatelets/anticoagulants

	SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLP/PIB
Aspirin	◆	◆	◆	◆	◆	◆	◆	◆
Clopidogrel	◆	◆	◆	●	◆	◆	◆	◆
Prasugrel	◆	◆	◆	■	◆	◆	◆	◆
Ticagrelor	◆	■	■	●	■	■	■	■
Apixaban	◆	■	■	●	■	■	■	■
Dabigatran	◆	■	■	■	■	■	●	●
Dalteparin	◆	◆	◆	◆	◆	◆	◆	◆
Edoxaban	◆	■	■	■	■	■	●	■
Enoxaparin	◆	◆	◆	◆	◆	◆	◆	◆
Rivaroxaban	◆	■	■	●	■	■	■	■
Warfarin	■	■	■	■	■	■	■	■

Colour Legend

◆ No clinically significant interaction expected.
■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r* + *DSV* ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *DCV* daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

4.6.9 Antiplatelets

Aspirin can be taken along with all HCV DAAs. A clinically significant interaction is also unlikely with clopidogrel and the DAAs with the exception of ritonavir-containing regimens. Clopidogrel is converted to its active metabolite by CYP3A4, 2B6, 2C19 and 1A2. Co-administration of clopidogrel (300 mg loading dose followed by 75 mg once daily) and ritonavir (100 mg twice daily) was investigated in 12 HCV-negative subjects in the presence of dasabuvir (250 mg single dose). Ritonavir significantly decreased the exposure of clopidogrel active metabolite by 51% and average platelet inhibition significantly decreased from 51% without ritonavir to 31% with ritonavir (mean difference 90% CI -27% to -12%). Maximal platelet inhibition was also reduced from 60% to 40% during concurrent ritonavir (mean difference 90% CI -29% to -11%) [59]. Therefore, co-administration with clopidogrel and OBV/PTV/r with or without DSV should be avoided due to the potential increased risk of atherothrombotic events.

Prasugrel and clopidogrel pharmacokinetics were also investigated in HIV-positive patients in the presence of boosted antiretroviral therapies, containing ritonavir or cobicistat. AUC of the active metabolites of clopidogrel and prasugrel were both significantly reduced (69% and 52% decreases, respectively) compared with healthy volunteers receiving antiplatelet therapy only. Interestingly, the reduced exposure led to insufficient platelet inhibition by clopidogrel (in 44% of the patients studied) but prasugrel continued to achieve potent platelet inhibition with, or without, ritonavir or cobicistat.

Ticagrelor is a substrate of both CYP3A4 and P-gp [60]. It is contraindicated with ritonavir-containing regimens due to potent CYP3A4 inhibition. The clinical significance of mild to moderate CYP3A4 or P-gp inhibition on ticagrelor, which has a narrow therapeutic index, is less clear. Therefore, in the case of the other currently available DAAs, if co-administration deemed necessary, then close monitoring of ticagrelor would be prudent. Ticagrelor is also a mild inhibitor of CYP3A4 and P-gp but a clinically significant effect on DAA concentrations is unlikely.

4.6.10 Anticoagulants

Warfarin is a mixture of enantiomers that are metabolised by different CYP P450 cytochromes. R-warfarin is metabolised by CYP1A2 and CYP3A4. The more potent, S-warfarin is metabolised primarily by CYP2C9. Ritonavir has both inhibitory and inducible effects on the enzymes involved in warfarin metabolism (CYP3A4 inhibition and CYP2C9/1A2 induction). In a pharmacokinetic study, co-administration of OBV/PTV/r and DSV with warfarin (5 mg single dose) had no significant effect on the plasma exposures of S-warfarin or R-warfarin (R-warfarin Cmax increased by 5%, but AUC and Cmin decreased by 12% and 6%; S-warfarin Cmax, AUC and Cmin decreased by 4%, 12% and 5%, respectively) [21, 22] However, published case reports have described marked reductions in international normalised ratio (INR) in two patients on warfarin starting

OBV/PTV/r and DSV with ribavirin [61, 62] In both cases, co-administration resulted in an increased warfarin dose by 125% from baseline. The effect of the interaction occurred around 1.5–2 weeks after initiation of OBV/PTV/r and DSV with ribavirin and the effect diminished after 2 weeks of stopping therapy, consistent with the expected time for induction/deinduction of hepatic enzymes. Therefore, caution is advised with co-administration of OBV/PTV/r and DSV with warfarin. Extremely close monitoring of the INR is recommended, taking into consideration the time it may take for enzyme induction/deinduction to occur. There is a single case report of ribavirin decreasing the anticoagulant effects of warfarin [63]. The mechanism behind this potential interaction is unclear and is not well established.

There are no clinically significant pharmacokinetic drug interactions predicted with warfarin and the other DAAs. However, fluctuations in INR values may occur in patients receiving warfarin concomitant with HCV treatment with any regimen as a result of improved liver function. Therefore, frequent monitoring is recommended during treatment and post-treatment follow-up [64].

The potential for interactions between HCV DAAs and direct-acting oral anticoagulants is complex. Rivaroxaban and apixaban are substrates of CYP3A4, p-gp and BCRP and are contraindicated with drugs that are potent inhibitors of both CYP3A4/p-gp. It is recommended that ritonavir, within the regimen OBV/PTV/r and DSV, should not be used with these drugs [65, 66]. Co-administration of rivaroxaban (10 mg OD) with ritonavir (600 mg BD) increased rivaroxaban AUC by 150% and Cmax by 60% and ritonavir is contraindicated in the product license for each drug [63, 67]. Other DAA regimens, which are mild/moderate inhibitors of these pathways, are likely to have a lesser impact [68]. However, any increase in drug levels may lead to an increased risk of bleeding and, in the absence of data, caution is recommended. A patient's individual risk of bleeding should be taken into account before co-administration is considered. Moderate to severe hepatic disease may be associated with coagulopathy and could lead to a substantial increase in bleeding risk. Moderate hepatic impairment (Child–Pugh B) affects the pharmacokinetics of rivaroxaban to a clinically relevant degree increasing AUC by 2.27-fold [69]. Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child–Pugh B or C [63]. Apixaban exposure was also increased in moderate hepatic impairment but to a lesser extent than with rivaroxaban (AUC increased by 1.09-fold) [70]. It may be used with caution in patients with Child–Pugh B but is not recommended in Child–Pugh C [62].

In some centres, anti-factor Xa activity levels (for rivaroxaban, apixaban or edoxaban) can be checked pre-treatment and during therapy to monitor for any altered drug exposure although the correlation between these levels and risk of bleeding/thrombosis is not well understood. In patients with higher bleeding risks, a switch to low molecular weight heparin for the duration of HCV therapy should be considered.

Dabigatran is metabolised by hydrolysis and is a substrate of UGT and p-gp. All HCV DAA regimens have some inhibitory effect on p-gp and, thus, have the potential to increase dabigatran exposure. Co-administration of dabigatran has

been studied with both glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir. Co-administration with both of these DAA regimens resulted in approximately a two- to threefold increase in dabigatran Cmax and AUC suggesting concomitant use should be avoided due to significant potential for bleeding complications [16, 34]. *Ritonavir alone has not been shown to significantly affect dabigatran levels* [71]. *However, the additive effect of p-gp and UGT inhibition by* OBV/PTV and DSV *in addition to ritonavir may have an impact on dabigatran exposure. In the absence of data, caution and close monitoring is recommended if dabigatran is used concomitantly with* OBV/PTV/r and DSV.

Pharmacokinetic studies have not been carried out with any HCV DAAs and edoxaban to date. It is a P-gp substrate and, like dabigatran, should be used with caution with most DAAs due to the potential for increased exposure. Edoxaban is not recommended for use with sofosbuvir/velpatasvir/voxilaprevir. The active metabolite of edoxaban is metabolised by OATP1B1 and its concentrations may be increased by velpatasvir and voxilaprevir due to inhibition of OATP1B1 [16].

4.6.11 Opioid Substitution Therapy (OST) and Illicit Drugs

People who inject drugs (PWID) and those who are prescribed OST such as methadone and buprenorphine +/− naloxone are a target demographic group for HCV treatment given their high HCV prevalence [72, 73] (Table 4.6). Real-world studies have confirmed treatment efficacy among people with recent illicit drug use with SVR 12 rates of 95% or greater [74, 75]. Therefore, the potential for drug–drug interactions with OST and illicit drugs should be taken into consideration when starting HCV DAAs. It is important to note that drug interaction studies are very limited in this area and predictive pharmacokinetic interactions from in vitro and in vivo drug metabolism data are usually needed. Many illicit drugs are substrates of one or more CYP450 enzymes; therefore, they can be susceptible to drug interactions if this pathway is affected. Unfortunately, the exact routes of metabolism are not always fully established with the added complexity if impurities are present which may cause unexpected interactions and toxicity. Another challenge for prescribers considering drug–drug interactions with HCV DAAs is the influx of novel substances being manufactured and sold. There is little knowledge of the chemical structure and metabolism of these substances. A thorough and non-judgemental drug history is essential.

4.6.12 Illicit/recreational Drugs

The landscape of drug interactions with HCV treatment and illicit and recreational drugs has changed dramatically with the more recently approved DAAs. Potent CYP3A4/possible 2D6 inhibition remains a concern with ritonavir-containing regimens but there are few issues with any of the other DAAs.

Table 4.6 Drug–drug interactions between HCV DAAs and OST/illicit drugs

	SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLP/PIB
Methadone	◆	◆	◆	◆	◆	◆	◆	◆
Buprenorphine	◆	▲	▲	■	◆	◆	▲	◆
Naloxone	◆	◆	◆	◆	◆	◆	◆	◆
Amphetamine	◆	◆	◆	■	◆	◆	◆	◆
Cannabis	◆	◆	◆	■	◆	◆	◆	◆
Cocaine	◆	◆	◆	■	◆	◆	◆	◆
Diamorphine (heroin)	◆	◆	◆	■	◆	◆	◆	◆
Diazepam	◆	◆	◆	■	◆	◆	◆	◆
Gamma-hydroxybutyrate (GHB)	◆	◆	◆	■	■	◆	◆	■
Ketamine	◆	◆	◆	■	◆	◆	◆	◆
MDMA (ecstasy)	◆	◆	◆	■	◆	◆	◆	◆
Mephedrone	◆	◆	◆	■	◆	◆	◆	◆
Methamphetamine	◆	◆	◆	■	◆	◆	◆	◆
Phencyclidine (PCP)	◆	◆	◆	■	◆	◆	◆	◆
Temazepam	◆	◆	◆	◆	◆	◆	◆	◆

Colour Legend

◆ No clinically significant interaction expected.
▲ Potential interaction predicted to be of weak intensity.
■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.
● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r + DSV* ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *DCV* daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

CYP3A4 is involved in the metabolism of many illicit drugs, to a greater (for example, ketamine and PCP) or lesser extent (for example, cocaine, diamorphine and tetrahydrocannabinol (THC), the active ingredient in cannabis) [76, 77]. Potent CYP3A4 inhibition by ritonavir-containing DAAs may increase exposure and subsequent increased risk of toxicity. Grazoprevir/elbasvir and glecaprevir/pibrentasvir are only weak inhibitors of CYP3A4 and so are unlikely to cause any clinically significant effect with the exception of narrow therapeutic range drugs, like GHB. The pharmacokinetics of GHB are not well understood. It does appear to show high first-pass metabolism, which is often mediated by the CYP450 system [73, 78]. Therefore, it is possible that drugs that inhibit or induce CYP enzymes may alter GHB concentrations. Given the narrow therapeutic index, and life-threatening toxicities associated with GHB, caution is advised with any DAAs which may inhibit CYP enzymes, such as OBV/PTV/r +/− DSV, grazopevir/elbasvir and glecaprevir/pibrentasvir. There is one reported case of near-fatal

reaction with symptoms consistent with GHB-toxicity in an HIV-positive patient which seemed likely to be related to saquinavir/ritonavir [79].

CYP2D6 is the principal enzyme involved in the metabolism of amphetamine, methamphetamine, MDMA and mephedrone [73]. Ritonavir is a known inhibitor of CYP2D6 at high doses and there is a case report of a fatal interaction in a patient taking MDMA concomitantly with ritonavir 600 mg twice daily for HIV infection [80, 81]. However, at lower doses, the effect on CYP2D6 is less pronounced. Pharmacokinetic studies have suggested relatively little to no effect on the CYP2D6 probe, desipramine at a ritonavir dose of 100 mg twice daily [82, 83]. Although the effect of low-dose ritonavir appears to be clinically irrelevant for the most part, it would be sensible to consider a possible interaction for drugs that are predominantly metabolised by CYP2D6 and have a narrow therapeutic index, particularly in the case of illicit/recreational drugs where dosing can be variable. None of the other available DAAs have an effect on 2D6 enzymes.

4.6.13 Opioid Substitution Therapies (OST)

Methadone, administered as a combination of the R- and S-isomers, appears to be metabolised by multiple CYP enzymes, including CYP3A4, 2B6 and 2C19. Buprenorphine is a CYP3A4 and CYP2C8 substrate and also undergoes glucuronidation, primarily carried out by UGT1A1 [84–90].

Pharmacokinetic studies evaluating the co-administration of methadone or buprenorphine/naloxone in combination with OBV/PTV/r and DSV were carried out in healthy volunteers [19]. R- or S-methadone exposure was not affected ($\leq$5% change in Cmax and AUC). Co-administration had a modest effect on naloxone exposures (18% and 28% increase in Cmax and AUC, respectively). In contrast, buprenorphine Cmax and AUC increased by 118% and 107%, respectively, and norbuprenorphine Cmax and AUC increased by 107% and 84%, respectively. This is likely due to UGT1A1 inhibition by OBV/PTV/r and DSV. There were no significant changes in pharmacodynamics measurements (e.g. pupil diameter, opioid withdrawal scale score or desire for drug) which suggested there was no clinical impact as a result of any change in drug levels. Thus, both methadone and buprenorphine/naloxone can be used with OBV/PTV/r and DSV without a priori dose adjustment, although monitoring for adverse effects may be prudent with buprenorphine, particularly in those with hepatic impairment.

There are no predicted significant interactions with any of the other DAA combinations and OST. Daclatasvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir and sofosbuvir have all been studied in combination with methadone and buprenorphine/naloxone [91–94]. No clinically meaningful effects on the pharmacokinetics of the OST drugs or DAAs were observed. Sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir may theoretically increase buprenorphine and norbuprenorphine levels due to p-gp inhibition. However, the clinical significance of this is unclear and co-administration has not been studied [46].

4.6.14 Contraceptives

The use of contraceptives is an important aspect of HCV treatment in females of childbearing potential. It is particularly essential if ribavirin is prescribed due to the teratogenicity of this drug (Table 4.7).

Ethinylestradiol (EE) containing contraceptives are contraindicated with OBV/PTV/r and DSV, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir due to the potential risk of alanine aminotransferase (ALT) elevations. The mechanism for this interaction is unclear. In a phase I clinical study, 5 of 21 healthy volunteers who received OBV/PTV/r and DSV in combination with EE plus norgestimate or norethindrone experienced Grade 3/4 ALT elevations. Four of the five subjects with these adverse events prematurely discontinued study drugs and the fifth subject discontinued study drugs when the study arm was stopped on Day 15. The ALT elevations were asymptomatic and normalised after discontinuation in all cases with no concurrent significant increase in bilirubin [95]. Other HCV DAAs are not expected to interact in this way [41]. Drug interaction studies investigating safety and tolerability of co-administration of grazoprevir/elbasvir with EE and levonorgestrel reported no increased incidence of adverse effects or liver function abnormalities and concluded that this combination can be safely co-administered with oral contraceptives [96].

Table 4.7 Drug–drug interactions between HCV DAAs and contraceptives

	SOF	SOF/LDV	SOF/VEL	OBV/PTV/r + DSV	GZR/EBR	DCV	S/V/V	GLP/PIB
Desogestrel (POP)	◆	◆	◆	■	◆	◆	◆	◆
Desogestrel (COC)	◆	◆	◆	●	◆	◆	●	●
Drospirenone (COC)	◆	◆	◆	●	◆	◆	◆	◆
Ethinylestradiol	◆	◆	◆	●	◆	◆	●	●
Levonorgestrel (POP)	◆	◆	◆	◆	◆	◆	◆	◆
Levonorgestrel (COC)	◆	◆	◆	●	◆	◆	●	●
Norethisterone [Norethindrone] (POP)	◆	◆	◆	◆	◆	◆	◆	◆
Norethisterone [Norethindrone] (COC)	◆	◆	◆	●	◆	◆	●	●

Colour Legend

◆ No clinically significant interaction expected.

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

● These drugs should not be co-administered.

Notes:

- *Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.*
- *The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.*

SOF sofosbuvir, *SOF/LDV* sofosbuvir/ledipasvir, *SOF/VEL* sofosbuvir/velpatasvir, *OBV/PTV/r + DSV* ritonavir-boosted paritaprevir/ombitasvir/dasabuvir, *GZR/EBR* grazoprevir/elbasvir, *DCV* daclatasvir, *S/V/V* sofosbuvir/velpatasvir/voxilaprevir, *GLE/PIB* glecaprevir/pibrentasvir

Progestogen-only contraception can generally be safely used in combination with HCV DAAs with no dose adjustment required. CYP450 enzyme pathways are involved in the metabolism of desogestrel, norethisterone and levonorgestrel. However, as most DAAs only have a mild impact or no effect on CYP450 enzymes, a clinically significant interaction is not expected. Glecaprevir/pibrentasvir has been studied with levonorgestrel and norgestimate (in combination with EE). Co-administration with norgestimate increased exposure of the active metabolites, norelgestromin and norgestrel, by 44% and 63%, respectively. Norgestrel exposure increased by 68% when levonorgestrel was given with glecaprevir/pibrentasvir. This observed increased exposure of progestogen metabolites are not expected to affect contraceptive efficacy [34]. Additionally, co-administration of EE and norgestimate with sofosbuvir/velpatasvir/voxilaprevir had no effect on Cmax, AUC or Cmin of ethinylestradiol, norelgestromin or norgestrel [16]. Ritonavir-containing regimens may be expected to have a more significant impact on progestogen levels. However, co-administration of OBV/PTV/r, and DSV with norethindrone did not affect norethindrone, ritonavir, OBV or DSV exposures ($\leq$17% reduction in Cmax and AUC). There were slight increases observed in PTV Cmax and AUC (24% and 23%, respectively) but these were deemed unlikely to be clinically significant [93]. Desogestrel has not been studied in combination with any DAA. It is a prodrug that requires activation to etonogestrel. Activation to etonogestrel is by CYP2C9 (and possibly CYP2C19); the metabolism of etonogestrel is mediated by CYP3A4. Co-administration with ritonavir is predicted to increase etonogestrel due to induction of CYP2C9 and inhibition of CYP3A4 [97]. Although contraceptive efficacy is unlikely to be affected, the magnitude of any increased exposure is difficult to predict and may lead to adverse effects. Caution is advised if desogestrel is to be used in combination with OBV/PTV/r and DSV [41]. Other HCV DAAs are unlikely to interact to any great extent and can be considered for use with desogestrel.

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Current Management of Patients with HCV Genotype 1

5

Tarik Asselah and Patrick Marcellin

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CHC	chronic hepatitis C
CKD	chronic kidney disease
DAAs	direct-acting antivirals
eGFR	estimated glomerular filtration rate
GT	genotype
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IDSA	Infectious Diseases Society of America
IFN	interferon
PEG-IFN	pegylated-interferon
PI	protease inhibitors
PWID	People who inject drugs
QD	once daily
RAV	resistance-associated variants
RBV	ribavirin
RdRp	RNA-dependent RNA polymerase
SVR	sustained virological response
EBV	elbasvir

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GLE	glecaprevir
GRZ	grazoprevir
LDV	ledipasvir
PIB	pibrentasvir
SOF	sofosbuvir
STR	single-tablet regimen
VEL	velpatasvir
VOX	voxilaprevir

5.1 Introduction

An impressive revolution has recently occurred with the availability of direct-acting antivirals (DAAs) with different mode of actions, leading to a high chance of cure and a favorable tolerability [1, 2]. The primary goal of treatment is to achieve a sustained virological response (SVR) defined as undetectable serum HCV RNA 12 weeks after the end of treatment [3]. An SVR has been shown to be durable and associated with the eradication of HCV infection confirmed by undetectable HCV RNA in the liver [4].

An SVR indicates that viral infection has been cured. In addition, viral eradication is associated with the reversal of cirrhosis and a significant improvement in clinical outcome and survival with a decreased incidence of hepatocellular carcinoma (HCC).

Persons with HCV compensated or decompensated cirrhosis who achieve an SVR can have significant reductions in hepatic venous pressure gradient during long-term follow-up [5]. The benefit to survival of DAAs in subjects with decompensated cirrhosis has been recently confirmed. Treatment with newly developed DAAs frequently improves perceived fatigue and patient-reported outcome [6].

5.2 Sofosbuvir/Velpatasvir (Epclusa)

Sofosbuvir (SOF) is an HCV non-structural (NS) 5B uridine nucleotide polymerase inhibitor, with a nanomolar in vitro activity against all HCV genotypes. It has a favourable safety profile and a high genetic barrier to resistance [7]. Velpatasvir (VEL) is a second-generation HCV NS5A inhibitor with antiviral activity against HCV replicons in genotypes 1 through 6 [8].

The combination of SOF/VEL for treating chronic HCV has been evaluated in several phase 3 studies [9, 10] ASTRAL-1, -2 and -3, each evaluated a once-daily, fixed-dose combination regimen of SOF/VEL for 12 weeks, and all together these studies included a broad range of HCV populations, including HCV genotypes 1–6 (Fig. 5.1). The overall response rate in more than 1000 patients was high, with 98% achieving SVR12 (Figure 5.1A). In particular, 323 among 328 (98%) patients with HCV infection achieved SVR12. Among the five patients who failed, there were: two relapses, two lost of follow-up, one discontinuation.

Treatment had a favourable safety and tolerability profile; 2% of patients experienced one or more serious adverse events (SAE) and no SAEs were considered study drug related. Two patients discontinued treatment due to AEs.

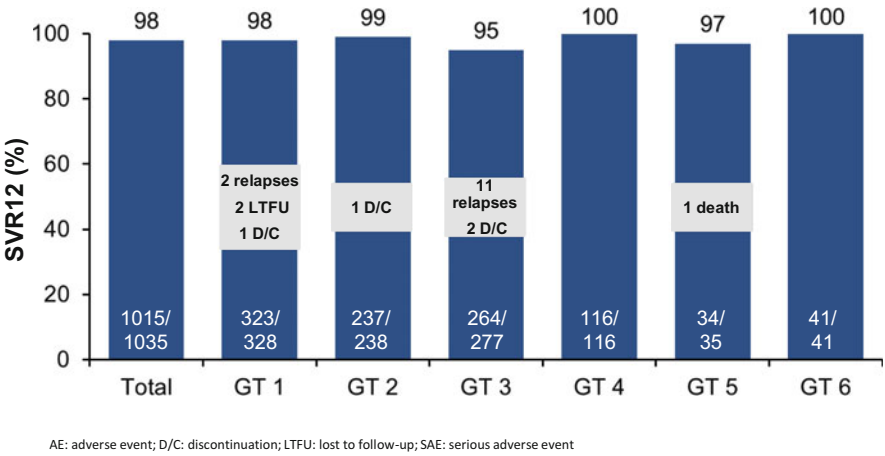


Fig. 5.1 SOF/VEL efficacy data. SOF/VEL for 12 weeks is highly effective across all genotypes (ASTRAL-1, ASTRAL-2 and ASTRAL-3). Two percent of patients experienced one or more SAE; no SAEs were considered to study drug related. Two patients discontinued treatment due to AEs

In a retrospective analysis of more than 500 patients, SOF/VEL was highly effective as a pan-genotypic treatment for HCV patients with advanced fibrosis or compensated cirrhosis, a population historically considered difficult to cure and with higher risks of safety issues [11] (Fig. 5.2). Treatment with SOF/VEL for 12 weeks resulted in an SVR12 in 98% of patients infected with HCV genotypes 1–6 (Fig. 5.2). In particular, SVR rates were 98% (167/170) in hepatitis C virus genotype 1 patients.

Sofosbuvir/Velpatasvir combination has been studied in patients with decompensated cirrhosis (Child–Pugh B) [12].

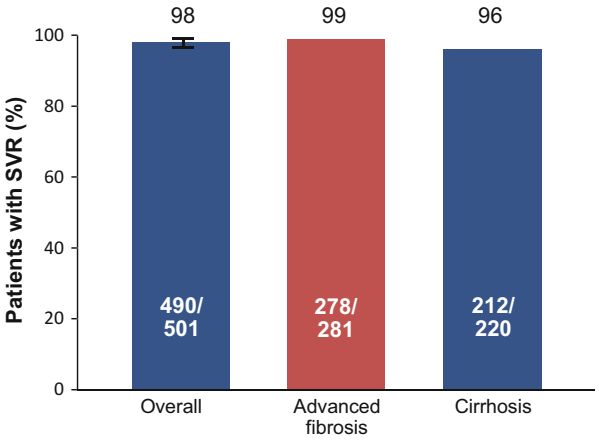


Fig. 5.2 SOF/VEL in patients with advanced fibrosis and cirrhosis. SOF/VEL for 12 weeks is highly effective in patients with advanced fibrosis and cirrhosis (ASTRAL 1, 2 and 3)

5.3 Sofosbuvir/Velpatasvir/Voxilaprevir (Vosevi)

Voxilaprevir (VOX) is a macrocyclic, pan-genotypic inhibitor of the NS3/4A protease with picomolar antiviral activity against HCV GT 1-6 and an improved resistance profile compared to first-wave protease inhibitors.

The POLARIS-2 trial enrolled patients infected with all HCV genotypes [13]. Compensated cirrhosis was allowed except for patients with HCV genotype 3 infection. Patients received either a fixed-dose combination of SOF/VEL/VOX once daily for 8 weeks or a fixed-dose combination of 400 mg of SOF/VEL once daily for 12 weeks. The overall SVR rate was 95% for the 8-week 3-DAAs regimen and 98% for the 12-week 2-DAAs regimen. Hence, the primary efficacy endpoint of non-inferiority (5% margin) was not met.

5.4 Glecaprevir/Pibrentasvir (Maviret)

Glecaprevir (GLE) is a potent NS3/4A protease inhibitor with nanomolar antiviral activity against HCV GT 1–6 and most known NS3 RASs [14]. Pibrentasvir (PIB) is an NS5A inhibitor with picomolar antiviral activity against HCV GT 1–6 and most NS5A RASs. This fixed-dose combination demonstrated synergistic antiviral activity, high barrier to resistance and a favourable safety profile (Figs. 5.3 and 5.4) [15, 16].

The efficacy and safety of the 8- and 12-week treatment with GLE/PIB in patients without cirrhosis with HCV genotype 1 or 3 infection was evaluated

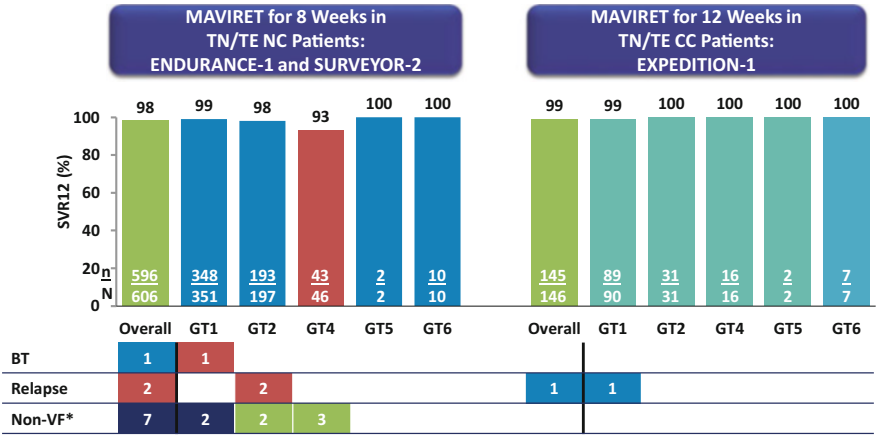
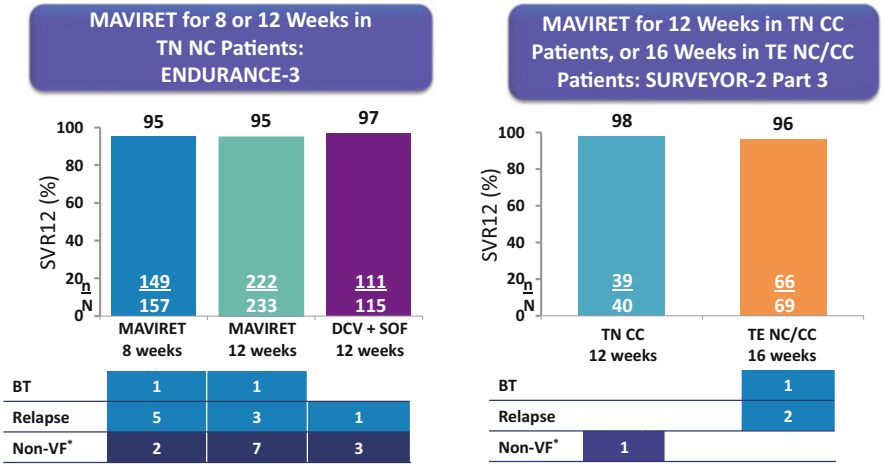


Fig. 5.3 Efficacy of GLE/PIB in Patients with HCV GT1, 2, 4–6 infection with or without compensated cirrhosis



All analyses are using the ITT population.
TN, treatment-naive; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN; BT, breakthrough; CC, compensated cirrhosis; NC, noncirrhotic; DCV, daclatasvir; ESRD, end-stage renal disease; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naive; VF, virologic failure.
*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

MAVIRET Summary of Product Characteristics; Accessed August 2017.

Fig. 5.4 Efficacy of GLE/PIB in patients with HCV GT3 infection with or without compensated cirrhosis

[16]. Endurance-1 and Endurance-3 were phase 3, randomised, open-label, multicentre studies. Patients with genotype 1 infection were randomised 1:1 to receive once-daily GLE/PIB for either 8 or 12 weeks. The SVR12 rate in genotype 1-infected patients was 99.1% in the 8-week group and 99.7% in the 12-week group. Adverse events led to discontinuation in $\leq$1% of patients.

Finally, in three Phase 3 studies, 8 weeks of treatment with GLE/PIB induced a high SVR12 in patients with chronic HCV infection without cirrhosis [15–17]. The drug combination had a safety profile comparable to 12 weeks of treatment with GLE/PIB. For patients with compensated cirrhosis, 8 weeks of treatment with GLE/PIB induced a high SVR12.

Another study evaluated patients with both HCV infection and advanced chronic kidney disease who have limited treatment options. A multicentre, open-label, phase 3 trial was performed to evaluate the efficacy and safety of treatment with GLE/PIB for 12 weeks in adults who had HCV genotypes 1, 2, 3, 4, 5 or 6 infection and also had compensated liver disease (with or without cirrhosis) with severe renal impairment, dependence on dialysis or both [18]. Patients had stage 4 or 5 chronic kidney disease and either had received no previous treatment for HCV infection or had received previous treatment. The SVR rate was 98% (102/104 patients). None of the patients had virological failures during treatment, and none had a virological relapse after the end of treatment. Adverse events were reported in at least 10% of the patients including pruritus, fatigue and nausea. Serious adverse events were reported in 24% of the patients. Four patients discontinued the trial treatment prematurely because of adverse events; three of these patients had an SVR.

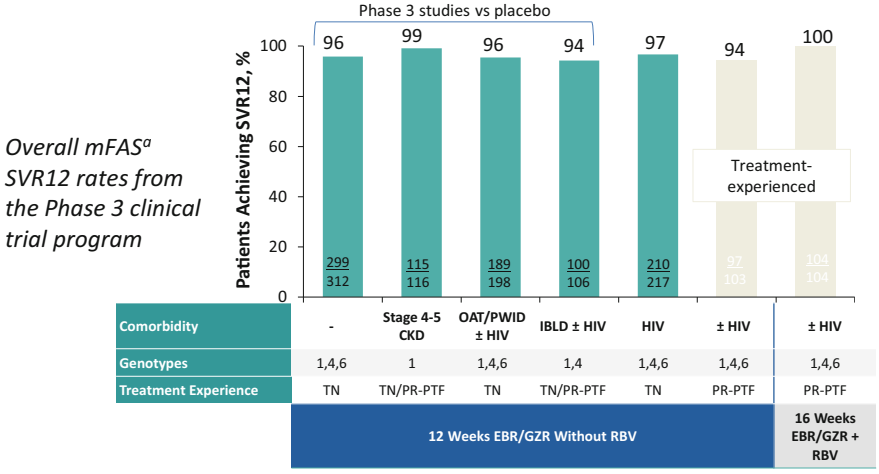
The authors concluded that treatment with GLE/PIB for 12 weeks resulted in a high rate of SVR in patients with stage 4 or 5 chronic kidney diseases and HCV infection.

5.5 Elbasvir/Grazoprevir (Zepatier)

Elbasvir (EBV), an NS5A inhibitor and Grazoprevir (GZR), an NS3/4A protease inhibitor have demonstrated high in vitro potency against HCV genotype 1 and 4 replicons. The C-Edge study evaluated the efficacy and safety profile of EBR/GZR in a Phase 3 study in treatment-naïve patients, with and without cirrhosis, with genotypes 1, 4 or 6 infection [19] (Fig. 5.5). SVR12 was achieved in 95% of patients. High efficacy was demonstrated in genotypes 1 and 4 HCV infection. High efficacy was reported in patients with compensated cirrhosis (SVR12 = 97.1%).

The C-Surfer study evaluated EBR/GZR in HCV-infected patients with creatinine clearance <30 mL/min, including patients on haemodialysis, chronic kidney disease (CKD) stage 4/5 (±haemodialysis dependence); CKD stage 4: eGFR 15–29 mL/min/1.73 m2; CKD stage 5: eGFR <15 mL/min/1.73 m2 or on dialysis, 22 targeting 20% non-haemodialysis patients [20]. In an ITT analysis, 94% (115/122) achieved an SVR12. In the modified full analysis set (non-virological failures excluded), 99% (115/116) achieved an SVR12.

Once-daily GZR/EBR for 12 weeks was highly effective for the treatment of HCV genotype 1 infection in patients with CKD stage 4/5. Efficacy is consistent



[a]mFAS excludes patients who failed for reasons unrelated to study medication.
EBR/GZR = elbasvir/grazoprevir; SVR12 = sustained virologic response 12 weeks after the cessation of treatment; CKD = chronic kidney disease; OAT = opioid agonist therapy; PWID = people who inject drugs; IBLD = inherited blood disorders; TN = treatment naive; HIV = human immunodeficiency virus; TE = treatment experienced; RBV = ribavirin; PR = peginterferon + ribavirin; PTF = prior-treatment failure; mFAS= modified full analysis set.

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Fig. 5.5 Efficacy of EBR/GZR in different patient populations

across different subpopulations: genotypes 1a and 1b, with diabetes, and patients on haemodialysis. Once-daily GZR/EBR for 12 weeks was generally well tolerated in this study population of patients with advanced kidney disease.

Furthermore, treatment with DAAs results in high rates of cure in people who inject drugs. A major study has demonstrated that patients with HCV infection who were receiving opiate agonist therapy and treated with EBR/GZR had high rates of SVR12, regardless of ongoing drug use [21]. In these studies, 0–3% of patients discontinued treatment because of adverse events. Compliance was excellent, even in patients using illicit drugs while on treatment. Risk of reinfection was rare.

5.6 Conclusion

The following regimens are recommended for patients with HCV genotype 1 infection:

- Sofosbuvir/Velpatasvir (Epclusa): The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg).
- **Glecaprevir/Pibrentasvir (Maviret):** The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. The duration is 8 weeks for patients without cirrhosis, and also for patients with compensated cirrhosis.
- **Elbasvir/Grazoprevir (Zepatier):** The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended for a duration of 12 weeks. In HCV genotype 1 naive with mild to moderate fibrosis, an 8 weeks duration provided high efficacy [22].

Simplification of the treatment regimen may expand the number of healthcare professionals who prescribe DAAs. This should lead to an increasing number of persons treated. Protease inhibitors are contra-indicated in patients with decompensated cirrhosis. Attention to drug interactions is an important treatment consideration.

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Patrick Marcellin has been a clinical investigator/speaker/consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme and Roche.

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Current Management of Patients with HCV Genotype 2

6

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6.1 Introduction

HCV genotype still represents the most important viral factor for selection of appropriate DAA regimen and treatment duration. However, the recent introduction of pangenotypic regimens has changed physicians' perspectives. Two different pangenotypic combinations are currently available, one based on the NS5B inhibitor sofosbuvir plus the NS5A inhibitor velpatasvir; the other, based on the pangenotypic NS3 and NS5A inhibitors glecaprevir and pibrentasvir. The former has the advantage of allowing the start of treatment without waiting for genotyping results as treatment duration and efficacy are similar across the different genotypes, the latter allows a duration of only 8 weeks in patients without cirrhosis.

This chapter will examine epidemiological and historical data on treatment of patients with GT2 infection before focusing on the current standard of care and on treatment of difficult subgroups of patients as decompensated cirrhosis and previous failure patients.

6.2 Epidemiological Data on GT2

HCV infection represents a global health problem. Worldwide approximately 71 million people are chronically infected. Overall, 15 million (13%) of the global infected population are GT2 [1–4]. In European countries, GT2 is less prevalent than genotypes 1 and 3 representing the third most frequent HCV genotype. It accounts for 10% of HCV chronic infections in Europe, picking to 27% in Italy. Outside of Europe, a higher prevalence has been reported in Southern Africa and in Asia where up to 30% of HCV-infected patients are GT2.

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6.3 Historical Evolution of GT2 Treatment

Peg-IFN and ribavirin have represented the standard of care for treatment of patients with chronic HCV infection until very recently. With that regimen, GT2 has generally been associated with higher antiviral treatment response rates compared to all other genotypes. Consequently, GT2 has been traditionally considered easy-to-treat [5, 6]. Not surprisingly, with the development of new DAA, the first IFN free combination based on the uridine nucleotide analogue sofosbuvir (a selective inhibitor of NS5B polymerase used as the backbone in several further DAA regimens) plus ribavirin, was just used in patients with GT2 and 3 infections. More than 500 naïve, interferon ineligible and previous failure patients with GT2 or 3 infections were treated in FISSION, POSITRON, and FUSION studies. Rates of SVR reported in this genotype were higher than 85%. Sofosbuvir and ribavirin combination resulted well tolerated and safe (Table 6.1) [7, 8].

Sofosbuvir and ribavirin regimen was genotype related, as it was indicated for GT2 and 3 and suboptimal for GT1. Therefore, at that time precise assessment of genotype before starting treatment was mandatory. The commercial hybridization assays of second generation are the most common genotype assessment method. However, the recent identification of 2k/1b variant, derived from one single recombination event most likely in the former Soviet Union and widespread in Europe due to migration flow, has been associated with sofosbuvir and ribavirin failure. In case of infection due to this variant, sequencing is required for correct genotyping. HCV sequencing for genotype assessment is not currently recommended [11], however, population-based assessment can be useful in case of mixed infections, indeterminate genotype or subtype.

With the availability of NS5A inhibitors, to be added to sofosbuvir in order to increase the efficacy over the combination with ribavirin, a first pangenotypic combination with the limitation of a low genetic barrier became available based on daclatasvir and sofosbuvir [10]. However, only a few patients with GT2 were included in the phase II study while phase III studies were missing. In addition, high costs limited the implementation of this regimen for the 24-week duration [12]. Real-life experience demonstrates high efficacy in patients with GT2 [13].

Table 6.1 First wave IFN-free treatment regimens and SVR in GT2 patients

	No. of Pts.	Duration, wks	SVR rates	References
Sofosbuvir + RBV (Fission)	73	12	94%	Lawitz et al. [7]
Sofosbuvir + RBV (Positron)	207	12	78%	Jacobson et al. [8]
Sofosbuvir + RBV (Fusion)	201	12 or 16	50% 73%	Jacobson et al. [8]
Sofosbuvir + Ribavirin (Valence)	73	12	93%	Zeuzem et al. [9]
Sofosbuvir + Daclatasvir	14	24	100%	Sulkowski et al. [10]
Sofosbuvir + Daclatasvir	14	24	93%	Sulkowski et al. [10]

Consequently, the real first pangenotypic regimen for patients with GT2 is represented by the fixed-dose SOF/VEL combination as once daily single pill. This pangenotypic regimen has reduced the risk of mistreating GT2 patients and has changed the approach to management and treatment. Assessment of the severity of the underlying liver disease remains essential to individualize treatment of patients with decompensated disease by adding ribavirin [14].

6.4 Genotype 2 Treatment: From Sofosbuvir and Ribavirin to Sofosbuvir and Daclatasvir

6.4.1 Sofosbuvir and Ribavirin

The combination of daily sofosbuvir (400 mg) and daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively) by now considered exceeded, was associated with SVR rates of 97% in naïve patients with GT2 infection after 12 weeks of treatment.

However, from the beginning of the oral DAA regimens era, a difference between cirrhotic and non-cirrhotic patients emerged even among the "easy-to-treat" GT2 patients. It was clear that patients with cirrhosis needed a longer treatment duration. Across three registration studies, FISSION in naïve, POSITRON in interferon-intolerant, and FUSION in treatment experienced, 30 GT2 patients with cirrhosis were treated with sofosbuvir and ribavirin. Among naïve (FISSION study), after 12 weeks of SOF/RBV, SVR rates were 93% for cirrhotic patients. In the POSITRON study, 16 of 17 GT2 cirrhotic patients never treated with IFN because intolerant achieved SVR (94%) [7, 8] (Table 6.1).

The impact of the regimen in previously treated patients was explored in the FUSION study. In fact, 68 patients with GT2 and history of a prior treatment failure were randomized to 12 or 16 weeks. While in non-cirrhotic patients the extended treatment did not increase SVR rates, in 19 patients with cirrhosis SVR were higher (78% vs 60%) after 16 weeks. Among 9 cirrhotic subjects treated for an extended duration, 7 reported SVR in contrast to 6 of 10 of those treated for 12 weeks. Finally, the VALENCE study evaluated 73 GT2 European patients, and 250 with genotype 3 infection. GT2 patients received 12 weeks, while genotype 3 received 24 weeks of treatment [9]. Overall, GT2 patients achieved an SVR of 93%. For treatment naïve, the presence of cirrhosis had no impact on SVR (97% vs 100%) (Table 6.1).

Of GT2 patients, only 11 were cirrhotic, and 9 of them were also treatment experienced. Among treatment experienced SVR were 94% for non-cirrhotic and 78% for cirrhotic patients. Although conclusions were limited by a small sample size, for GT2 the number of cirrhotic patients included in the studies was considered enough to release recommendations. European and American Guidelines recommended to extend the duration of therapy to 16 or 20 weeks in patients with cirrhosis, in particular, if prior failures [12, 15].

Real-life data from Germany suggest that SVR may be lower in real life than in the studies in particular subjects with cirrhosis [16]. However, another study from

Italy demonstrated SVR rates comparable to those reported in the registration studies, provided that ribavirin dosages were based on body weight and duration of treatment individualized on the severity of liver disease [17].

Finally, a viral factor emerged as a potential confounder. The 2k/1b chimera variant was found in countries with high migration flow as Germany [18] and investigated in epidemiological studies to establish the potential risk of non-response in subjects that commercial genotyping testing considered as genotype 2. The variant was associated with relapse in up to 74% of cases after treatment with sofosbuvir and ribavirin in patients from Germany.

6.4.2 Sofosbuvir and Daclatasvir

Inhibitors of HCV NS5A represent a class of compounds developed to target an RNA-binding phosphoprotein whose phosphorylation state plays an important role in viral RNA replication, virus assembly, and packaging. NS5A inhibitors showed favorable efficacy across all major genotypes. However, pre-existing resistance-associated substitutions (RAS) in NS5A region may still decrease SVR rates. In particular, residues 30, 31, and 93 are considered the major sites associated with resistance to NS5A inhibitors. In patients with GT2, the most frequently described are RASs at positions 28, 30, 31, 58, and 92 [19].

Daclatasvir was the firstly introduced NS5A inhibitor. GT2 patients were treated using sofosbuvir and daclatasvir (60 mg daily) combination in several real-life studies even in the absence of registration studies. Evaluated at the first time in Al1444-40 in only 26 patients, for a treatment duration of 24 weeks, it was associated with SVR of 96% (Table 6.1). However, patients with cirrhosis were excluded from the study [10]. The large European Compassionate Use Program on 485 patients with advanced liver disease promoted by BMS included only 2 patients with genotype 2 [20].

A small group of 20 cirrhotic patients including those with decompensated disease received sofosbuvir and daclatasvir either for 24 or for 12 weeks within an open-label real-life study at our center, all attained SVR suggesting a limited impact of the treatment duration on SVR for GT2 patients with advanced disease [13]. Daclatasvir plus sofosbuvir association was recommended by EASL for 12 weeks in patients with or without cirrhosis [12].

The other largely used NS5A inhibitor is ledipasvir. It has been approved for use at the dosage of 90 mg in fixed-dose combination with sofosbuvir. The combination of sofosbuvir and ledipasvir was not formally evaluated in patients with GT2 infection on the basis of low activity in vitro. Indeed, in comparison with genotype 1a, where ledipasvir's EC50 values are 31 pM, the corresponding EC50 were 21 nM against GT2a replicon with NS5A L31, and 249 nM against the genotype 2a replicon with L31M substitution, respectively [21]. However, recently, a phase 2 open-label study including 26 patients from New Zealand, a few of them with cirrhosis, demonstrated SVR rates of 96% after 12 weeks of sofosbuvir and ledipasvir [22].

6.4.3 GT2 Treatment Using the Pangenotypic Combination of SOF/VEL

EASL guidelines released in 2016 recommend SOF/VEL as the first option and daclatasvir/sofosbuvir as an alternative [12]. SOF/VEL was recommended at a standard dosage and duration regardless of the presence of compensated cirrhosis and prior failure for patients with GT2 without ribavirin. [23, 24].

Velpatasvir, former GS-5816, is a second-generation NS5A inhibitor that has potent in vitro antiviral activity across all HCV genotypes. The co-administration of SOF/VEL for 12 weeks without ribavirin resulted in SVR12 of 100% in 104 GT2 patients included in the ASTRAL-1 study (Table 6.2). Moreover, in an open-label study entirely dedicated to GT2 patients, the ASTRAL-2 study, a total of 240 patients, 14% of whom with cirrhosis and 14% with treatment failure history were randomized in the ratio of 1:1 to SOF/VEL for 12 weeks or SOF/RBV. SVR of 99% were reported for SOF/VEL as compared to 94% for sofosbuvir/ribavirin (Table 6.2). The only patient who did not achieve SVR among SOF/VEL treated patients was a 57-year-old man who discontinued treatment after one dose due to anxiety, headache and difficulties in concentrating.

At the first time, the presence of cirrhosis did not represent a negative predictor of lower response rates, as shown by SVR of 99% regardless of cirrhosis or prior treatment failure. These results were also confirmed in real-world experience [26] (Fig. 6.1).

Despite the presence of NS5A resistance-associated substitutions as L31M in 51% of patients and of NS5B RASs in 10%, no virological failure was reported [27].

Of interest, these excellent efficacy results were combined with high tolerability. In the ASTRAL-2, rates of adverse events were lower among patients receiving SOF/VEL than among those receiving sofosbuvir/ribavirin. Fatigue, headache, and nausea were the most frequently reported side effects after SOF/VEL. Two deaths were reported during the follow-up and deemed not related to the study drugs (due to a cardiac arrest and to complication of lung cancer metastasis, respectively) (Table 6.2).

This combination will definitively solve the issue of ribavirin tolerability and treatment duration in patients with GT2. Indeed, ribavirin used with sofosbuvir—although better tolerated than with interferon—was associated with treatment discontinuations mostly in patients with decompensated liver disease. Although patients with cirrhosis were enrolled in both ASTRAL-1 and ASTRAL-2, patients with decompensated disease were excluded from these studies and evaluated in a dedicated study named ASTRAL-4.

Table 6.2 Pangenotypic regimens currently used in GT2 patients and SVR rates

Study	No. of Pts.	Duration, wks	SVR rates
SOF/VEL (Feld et al. [23])	104	12	100%
SOF/VEL (Foster et al. [24])	132	12	99%
Gle/Pib (Kwo et al. [25])	130	8–12	96–98%

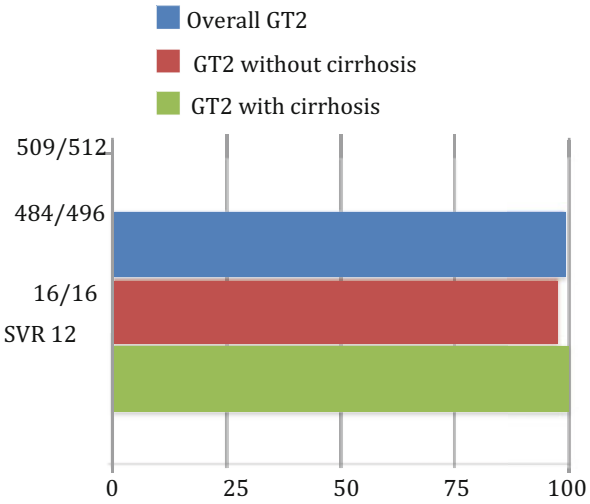

Fig. 6.1 Percentage of patients with GT2 achieving SVR12 in an Italian real-world study including 512 patients treated with SOF/VEL [27]

6.4.4 Glecaprevir/Pibrentasvir

SURVEYOR I and II were dose ranging phase II multicenter open-label studies on Gle/Pib in genotypes 1–6 without cirrhosis. Of 449 patients, 29% were GT2, they were treated for 8 or 12 weeks with or without ribavirin. For GT2 patients treated for 12 weeks, the SVR rate was 96% with 300 mg of Gle co-formulated with 100 mg of Pib. For patients treated for 8 weeks, 98% SVR rates were registered [25] (Table 6.2).

In the EXPEDITION II part 4 study, 34 GT2 cirrhotics received 12 weeks of Gle/Pib. All achieved SVR [28]. No patients discontinued study drugs; one patient died due to cerebral hemorrhage [28].

In an integrated analysis of patients treated with Gle/Pib in the various phase II and III studies presented at EASL 2017, 197 of 828 patients with genotype 2 received 8-week treatment, and 234 of 1076 were enrolled to 12 weeks [28]. These patients did not have cirrhosis. Patients with genotype 2 who received 8- and 12-week treatments achieved 99% and 100% SVR, respectively. Across all the genotype Gle/Pib for 8 weeks yielded SVR12 comparable to treatment for 12 weeks. Gle/Pib was well tolerated regardless of treatment duration, but it should be considered that cirrhotic patients were excluded from this study. It should be emphasized that presence of NS3 RAS combined with NS5A RAS at baseline significantly decreases SVR12.

The combination was shown safe and well tolerated. No patients discontinued treatment due to adverse events. No deaths occurred during the treatment period or during the follow-up [29].

6.4.5 Sofosbuvir/Velpatasvir/Voxilaprevir

Polaris-2 study compared 8 weeks of triple fixed-dose combination of sofosbuvir 400 mg plus velpatasvir 100 mg and voxilaprevir 100 mg (SOF/VEL/VOX) as fixed-dose combination for 12 weeks in patients who had never been exposed to DAA, with or without cirrhosis. The study included patients across all genotypes, but genotype 3 cirrhotics. The aim was to investigate whether triple combination for 8 weeks is inferior to dual combination for 12 weeks. Over 900 patients were included. SVR were 95% after SOF/VEL/VOX and 98% after SOF/VEL. Overall, the study failed to demonstrate that the triple combination for 8 weeks is not inferior to SOF/VEL for 12 weeks. The difference in SVR was mainly due to genotype 1a. SVR in patients with genotype 2 infection resulted similar between the two regimens, 92% (61/63) in naïve patients treated for 8 weeks compared to 100% after 12 weeks of SOF/VEL [30].

The most frequent adverse events associated with triple therapy were diarrhea and nausea. These side effects were mild and no treatment discontinuations due to side effects were registered.

6.4.6 Drug-to-Drug Interactions (DDI)

Many HCV infected patients take a number of co-medications related to concomitant diseases. An estimated risk of drug-to-drug interactions in 10% of subjects receiving DAA should be considered. However, this represents a mean risk as not all the combinations show a similar DDI profile, the highest being that related to protease inhibitors. Among, DDI the most relevant are those related to drug metabolism. CYP450 a microsomal superfamily of isoenzymes that catalyze the oxidation of many drugs represents the main site of DDIs. CYP450 can be induced or inhibited by several drugs, with induction resulting in a reduction of concentration of substrates and inhibition of substrates, with increase of substrates concentration. Velpatasvir has shown a limited number of DDI. Velpatasvir is a substrate of CYP2B6, 2C8, and CYP34A. Therefore, drugs inducing these enzymes may reduce velpatasvir levels leading to sub-therapeutic concentrations and risk of resistance development. Among CYP450 inducers, anticonvulsants, antimycobacterials, and no-nucleoside reverse inhibitors, including efavirenz, tenofovir, and emtricitabine need to be avoided. Velpatasvir acts as perpetrator for pravastatin and rosuvastatin, therefore both can increase Velpatasvir AUC. No clinically significant drug interactions have been observed with atazanavir/ritonavir and sofosbuvir/velpatasvir [24]. Velpatasvir is responsible of digoxin AUC increases.

Different DDI profile is associated with Gle/Pic. Glecaprevir is metabolized by CYP3A4, 2C8, and 2B6 and cannot be administered in patients taking dabigatran etexilate as well as rifampicin and carbamazepine. Anticonvulsants like phenobarbital, fenitoina, and primidone are not permitted. The other well-known contraindication is for Saint John wort. Estroprogestinic are not allowed with Gle/Pib. Another

class of drugs inducing DDI is statins. Simvastatin and pravastatin are contraindicated with Gle/Pib [25, 27].

Drug interactions based on altered metabolism are not the only DDI. Some membrane transporters have been identified as responsible for DDI in DAA treatment. Among them P-gp and organic anion transporters polypeptides, OATP. Velpatasvir demonstrated interactions with P-gp [24].

Finally, medications that raise gastric pH will likely decrease concentrations of VEL [24]. In patients taking PPI, 40 mg of omeprazole is not allowed with any combination, also with Gel/Pib dosages need to be adjusted to 20 mg [25, 27]. PPI can be administered at least four hours after sofosbuvir/velpatasvir is taken with food.

The use of amiodarone with sofosbuvir is contraindicated as it has been associated with bradycardia. Potential interaction can be expected with Gle/Pib [27].

DDI with SOF/VEL/VOX triple combinations are those already reported for sofosbuvir/velpatasvir. Acid reducing agents increasing gastric PH are expected to decrease velpatasvir concentrations, therefore, for PPI co-administration risks are similar to those of sofosbuvir/velpatasvir. Co-administration with amiodarone is not recommended with voxilaprevir. Rifampin and rifabutin are contraindicated because they may decrease SOF/VEL concentrations while increasing voxilaprevir. Voxilaprevir levels may increase for co-administration with atazanavir or lopinavir. Levels of statins may increase when co-administered with sofosbuvir/velpatasvir/voxilaprevir. Regarding immunosuppressive drugs, ciclosporin may increase voxilaprevir levels.

6.4.7 GT2 Patients with Decompensated Cirrhosis

The treatment paradigm for HCV decompensated patients underwent great changes after the discovery of DAA. The issue of treatment access in patients with decompensated cirrhosis who in the past could not be treated due to the Interferon side effects, was reduced by the availability of safe and tolerated DAA regimens. For Child-Pugh-Turcotte C, limited sample size in the studies affect generalization of the results.

Patients with CPT class B cirrhosis of genotypes 1–6 were enrolled into an open-label study on sofosbuvir 400 mg and velpatasvir 100 mg as a fixed-dose combination single pill once daily administration with or without ribavirin. Two hundred twenty-five patients were randomized 1:1:1 to sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir/ribavirin for 12 weeks, or sofosbuvir/velpatasvir for 24 weeks. Overall, 12 patients with genotype 2 were enrolled, 4 in each arm [31]. Patients who received sofosbuvir/velpatasvir for 12 weeks with or without ribavirin achieved SVR12, whereas 3 of 4 of those treated with sofosbuvir/velpatasvir for 24 weeks achieved SVR12. The number of patients with genotype 2 infection in this study were too small to allow firm conclusions on the best regimen for genotype 2 decompensated cirrhotic patients. However, at variance with genotype 3, for GT2 patients, SVR were high in all the treatment arms. The limitation of

this multicenter randomized, phase III study in decompensated cirrhotics was that the whole study was not powered to detect significant differences among the three treatment groups [31].

The safety profile of this regimen was comparable across the three study arms although rates of anemia and treatment discontinuations were marginally increased in the group of subjects who were treated with ribavirin. In patients with decompensated cirrhosis included in SOLAR1 and SOLAR 2 studies [32, 33], the dosage of ribavirin used since the start of treatment was a full dose based on body weight higher or lower than 75 kg, instead of a reduced half dosage to be increased according to tolerability as in other combinations.

In this decompensated subject population, due to the limited experience gathered in the registration studies, a close monitoring while on treatment will be required in real life, regardless of genotype.

In the absence of new drugs in development and given that decompensated patients cannot be treated with combinations including protease inhibitors, it can be expected that the answer to the question on what is the best regimen in subjects with decompensated disease including GT2 remains a prerogative of cohort studies. Difficult-to-treat patients may be best served by individualized regimens under the care of a specialist. The population of patients who may require individualized therapy but for whom evidence-based treatment data are limited includes, in addition to patients with decompensated cirrhosis, patients with renal failure, and in particular patients on hemodialysis and patients with a history of organ transplant on immunosuppression or other conditions resulting in being immunocompromised.

6.4.8 Re-treatment of GT2 Patients after DAA Failure

Overall, no more than 3–4% of patients treated with the current DAA regimens experience virological failure. Effective re-treatment strategies for patients who have previously failed HCV therapy containing DAA are available. The POLARIS program investigated the impact of the combination of sofosbuvir/velpatasvir/voxilaprevir as a fixed dose in a single daily pill in patients with a history of DAA failures. The combination formulated as fixed-dose single pill included, in addition to the backbone of sofosbuvir, the NS5A inhibitor velpatasvir investigated in the ASTRAL program and the second-generation NS3 pangenotypic inhibitor voxilaprevir [34].

Two studies from this program investigated patients who had failed a previous course with DAA. In Polaris 1, 263 patients who had failed NS5A inhibitors, of whom 5 with genotype 2 were enrolled in 12-week treatment. They were compared with a placebo arm that did not include genotype 2 subjects [33]. In POLARIS-4, sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 12 weeks was compared to SOF/VEL for 12 weeks. POLARIS-4 included overall 182 patients in SOF/VEL/VOX and 151 in the control arm with SOF/VEL [34]. Thirty-one and 33 GT2 patients, respectively, were randomized to either regimen. In POLARIS-1, rates of SVR for genotype 2 was 100%. In POLARIS-4, 100% of GT2 patients on

SOF/VEL/VOX achieved SVR, as compared to 97% of patients in SOF/VEL arm [35]. Thus, in POLARIS-4, a single patient with genotype 2 who received the SOF/VEL combination but none in SOF/VEL/VOX arm experienced a relapse. The number of patients who discontinued treatment and the number of subjects with serious side effects were comparable between arms containing SOF/VEL/VOX or placebo in POLARIS-1, and between SOF/VEL/VOX or SOF/VEL in POLARIS-4 [36].

The presence at baseline of RAS conferring resistance had no effects on SVR proving that SOF/VEL/VOX is an effective regimen in patients with prior DAA failure history.

The combination of Gle/Pib explored in the Magellan study for re-treatment did not evaluate GT2. Based on data from Surveyor II, this combination can be used for 12 weeks in patients who failed a previous sofosbuvir/ribavirin course but not in other DAA failures.

6.4.9 Treatment of Patients with Kidney Failure

Gle/Pib excretion is independent of kidney excretion. The Expedition-4 study evaluated this combination for 12 weeks in naïve, interferon or sofosbuvir treated patients with stages 4 and 5 chronic kidney disease. In this study, of 104 patients up to 82% were on hemodialysis. SVR was achieved by 82% [37]. No virological failure was registered. Adverse events reported in at least 10% of patients were pruritus, fatigue, and nausea. Serious adverse events were registered in 24% of patients. Four patients discontinued treatment for adverse events, three of them achieved SVR. Thus, a pangenotypic regimen is now available for patients with chronic stages 4 and 5 kidney disease.

6.5 Future Treatments

A further shortening of treatment duration was pursued by 2 additional pangenotypic regimens whose development was discontinued. The combination of odalasvir/Al-333 and simeprevir, respectively NS5A, non-nucleotidic and NS3 inhibitor compounds was explored in the OMEGA study in 300 patients either naive or PegInterferon experienced [38]. However, due to a relapse in patients with subtype 2a/c of genotype 2 this regimen will not reach the market [35].

A phase II study explored the new NS5B inhibitor, uprifosbuvir plus pangenotypic NS5A inhibitor, ruzasvir plus the NS3 inhibitor grazoprevir in patients with different genotype including genotype 2. Although in phase 3 studies this combination has been evaluated only in genotype 1 patients [39], for commercial reasons it will not reach the market.

6.6 Conclusions/Statements

Currently, pangenotypic regimens based on SOF/VEL or Gle/Pib combination are associated with extremely high rates of virological response in patients with HCV GT2 infection never treated before or for prior Peg-IFN and RBV failure patients. The most common subpopulation of patients with HCV infection is represented by non-cirrhotic. These patients will undergo treatment without genotyping assessment. Drug-to-drug interactions rather than the severity of liver disease will drive physician's choices. After DAA failure, the combination of SOF/VEL/VOX is recommended as the treatment of choice in GT2 patients, as well as in all the other genotypes.

In patients with GT2 and decompensated liver disease, SOF/VEL will be the best treatment option; for patients with kidney failure Gle/Pib combination represents the ideal treatment.

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Current Management of HCV Genotype 3 Infection

7

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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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Current Management of Patients with HCV Genotype 4

8

Tarik Asselah

Abbreviations

AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CHC	Chronic hepatitis C
CKD	Chronic kidney disease
DAAs	Direct-acting antivirals
EBV	Elbasvir
eGFR	Estimated glomerular filtration rate
GLE	Glecaprevir
GRZ	Grazoprevir
GT	Genotype
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IDSA	Infectious Diseases Society of America
IFN	Interferon
LDV	Ledipasvir
PEG-IFN	Pegylated interferon
PI	Protease inhibitors
PIB	Pibrentasvir
PWID	People who inject drugs
QD	Once daily

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RAV	Resistance-associated variants
RBV	Ribavirin
RdRp	RNA-dependent RNA polymerase
SOF	Sofosbuvir
STR	Single-tablet regimen
SVR	Sustained virological response
VEL	Velpatasvir
VOX	Voxilaprevir

8.1 Introduction

There is an increasing prevalence of HCV GT4 infection. Approximately 15% of HCV infections worldwide are due to GT4 [1] (Fig. 8.1). HCV GT4 is endemic in the Middle East and Africa, with increasing prevalence in Europe, Asia, and North America with increasing migration [1]. HCV genotype 4 is responsible for around 10%–25% of HCV infections in Albania, Belarus, Belgium, Greece, Montenegro, the Netherlands, Portugal, and Switzerland [2]. The majority of these people worldwide are likely to be treatment naive and noncirrhotic.

8.2 Direct-Acting Antivirals for HCV GT4

DAA with different viral targets (NS3 protease inhibitors, nucleoside/nucleotide analogs, and non-nucleoside inhibitors of the RNA-dependent RNA polymerase and NS5A inhibitors) have been developed [3] in combination and lead to high efficacy, reduced risk of resistance, and shortened treatment duration (Fig. 8.2).

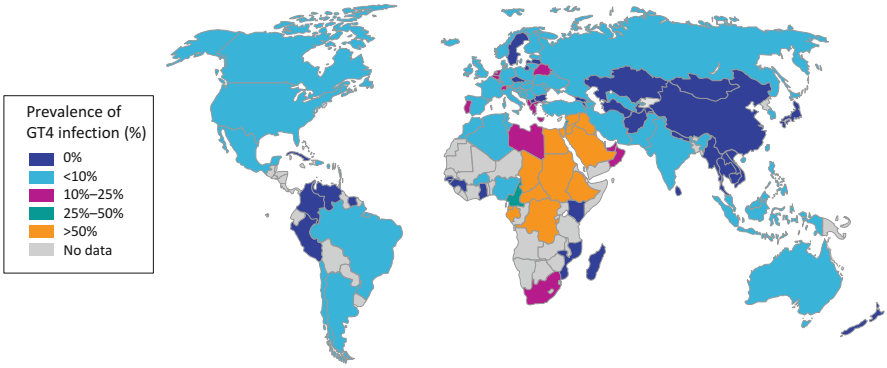
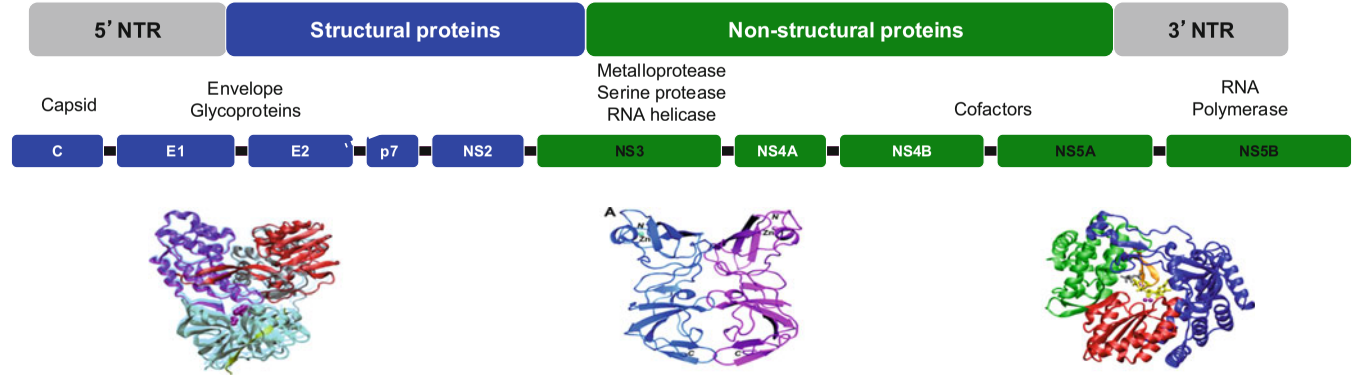


Fig. 8.1 Prevalence of HCV genotype 4 worldwide (%) (references: Asselah T et al. J Hepatol. 2018;68:814–826. Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol. 2017;2 (3): 161–763)



NS3	NS5A	NS5B
Grazoprevir (GZR) Glecaprevir (GLE) Voxilaprevir (VOX)	Ledipasvir (LDV) Elbasvir(EBR) Velpatasvir (VEL) Pibrentasvir (PIB)	Sofosbuvir (SOF)

Fig. 8.2 Mode of actions of recently approved direct-acting antivirals

8.3 Sofosbuvir-Based Regimen

8.3.1 Sofosbuvir/Ledipasvir

The HCV nonstructural (NS) 5B uridine nucleotide polymerase inhibitor, sofosbuvir (SOF), has activity against all HCV genotypes with a favorable safety profile and a high genetic barrier to resistance [4]. The HCV NS5A inhibitor, ledipasvir (LDV), has activity against all HCV genotypes with a favorable safety profile. SOF/VEL is available as single-tablet regimen (STR) once daily, orally, and is approved for HCV genotype 4 infection one pill a day for 12 weeks.

In a phase 2, open-label study, 44 patients (22 treatment naive and 22 treatment experienced) received LDV/SOF orally once daily for 12 weeks [5]. HCV genotype 4 subtypes were correctly represented. Ten patients (10/44; 23%) had compensated cirrhosis. All 44 patients completed the full 12 weeks of dosing, and there was no loss of follow-up. The SVR12 rate was 93% (41 of 44; 95% confidence interval, 81–99). SVR12 rates were similar between treatment-naive (95%; 21 of 22) and treatment-experienced (91%; 20 of 22) patients. All three patients who did not achieve SVR12 had virological relapse within 4 weeks of the end of treatment; all three had baseline HCV RNA $>$ 800,000 IU/mL, a non-CC IL-28B genotype, and pretreatment NS5A resistance-associated variants. None of the patients who relapsed had cirrhosis.

Phenotypic assessment of 56 HCV NS5A patient isolates from various GT4 subtypes indicated that ledipasvir had high potency for the common subtypes 4a/d and subtypes 4c/f/k/l/m/n/o/p/r/t despite the presence of resistance-associated substitutions (RASs) [6]. The 2 GT4r infected patients who had virologic relapse had rare triple RASs.

8.3.2 Sofosbuvir/Velpatasvir

Velpatasvir (VEL) is a second-generation pangenotypic HCV NS5A inhibitor with antiviral activity against most NS5 resistance-associated variants. In the phase 3 ASTRAL-1 trial, all the 116 patients with HCV-GT4 treated with SOF/VEL achieved SVR [7]. We recently analyzed 501 patients from 3 large phase 3 trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) with compensated cirrhosis (Metavir F4) or advanced fibrosis (F3) who received SOF/VEL for 12 weeks. Again all 60 patients with HCV GT4 infection and compensated cirrhosis or advanced fibrosis achieved SVR [8]. Finally, for patients with HCV GT4 infection including those with compensated cirrhosis, SOF/VEL treatment for 12 weeks is recommended.

8.3.3 Sofosbuvir/Velpatasvir/Voxilaprevir

Voxilaprevir (VOX) is a second-generation macrocyclic, pangenotypic inhibitor of the NS3/4A protease with activity against HCV GT 1-6 and an improved resistance profile when compared to first-generation protease inhibitors.

In the POLARIS-2 trial, patients received either a fixed-dose combination of 400 mg of SOF, 100 mg of VEL, plus 100 mg of VOX once daily for 8 weeks or a fixed-dose combination of 400 mg of SOF plus 100 mg of VEL once daily for 12 weeks [9]. The overall SVR rate was 95% for the 8-week 3-DAA regimen and 98% for the 12-week 2-DAA regimen. The primary efficacy endpoint of non-inferiority (5% margin) was not met.

The SVR rate for GT4 was 94% for the 8-week 3-DAA regimen and 98% for the 12-week 2-DAA regimen. Results of sofosbuvir-based regimen for HCV genotype 4 are represented in Fig. 8.3.

8.3.4 Glecaprevir-Pibrentasvir

Glecaprevir (GLE) is a potent NS3/4A protease inhibitor with nanomolar antiviral activity against HCV GT 1-6 and most known NS3 RASs. Pibrentasvir (PIB) is an NS5A inhibitor with picomolar antiviral activity against HCV GT 1-6 and most NS5A RASs. This fixed-dose combination demonstrates synergistic antiviral activity and a high barrier to resistance [10].

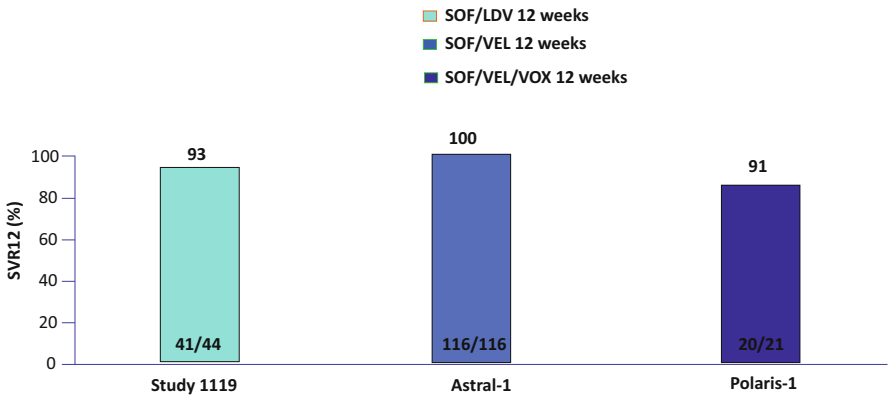


Fig. 8.3 Sofosbuvir-based regimen approved for HCV genotype 4 (references: Abergel A, Metivier S, Samuel D, Jiang D, Kersey K, Pang PS et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology. 2016 Oct; 64 (4):1049–56. Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015; 373: 2599–607. Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG et al. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir In Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology, 2017; 153(1):113–122)

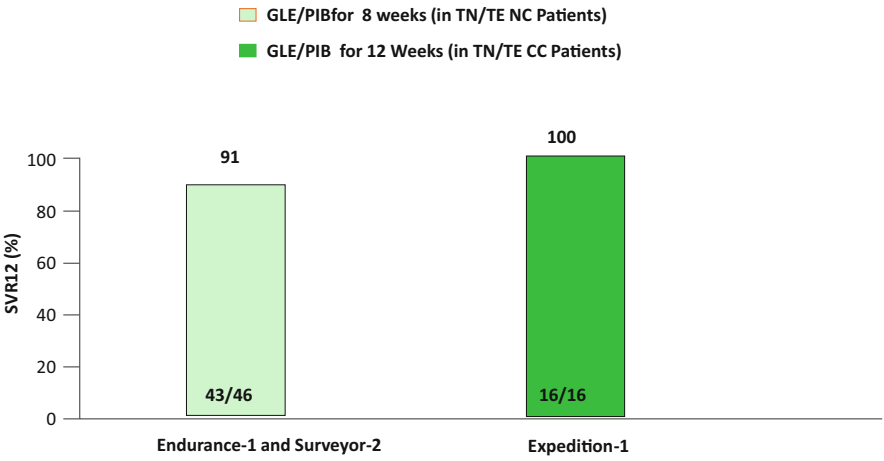


Fig. 8.4 Glecaprevir/pibrentasvir regimen approved for HCV genotype 4 (reference: MAVIRET Summary of Product Characteristics; Accessed August 2017. Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y et al. Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Patients with HCV Genotype 2, 4, 5, or 6 Infection Without Cirrhosis. Clin Gastroenterol Hepatol. 2017, in press)

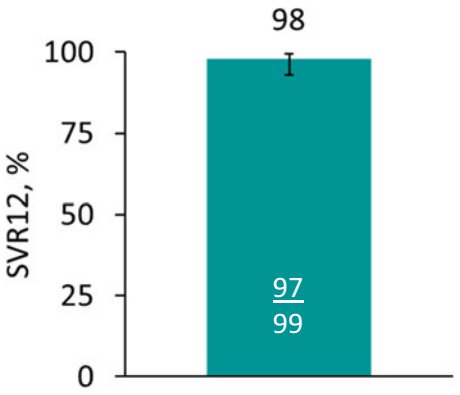
The efficacy and safety of 8-week and 12-week GLE/PIB treatment in noncirrhotic patients with HCV GT4, 5, or 6 infection were reported recently (Surveyor-II, Part 4 and Endurance-4) [11].

The SVR12 rate (ITT population) in patients with GT4 infection treated for 12 weeks was 99% (75/76) and 93% (43/46) for 8 weeks, with no virologic failures. The SVR12 rate (mITT population) was 100% (75/75) for 12 weeks and 100% (43/43) for 8 weeks. Results of GLE/PIB regimen for HCV genotype 4 are represented in Fig. 8.4. Finally, for patients with HCV GT4 infection including those with compensated cirrhosis, GLE/PIB treatment for 8 weeks is recommended.

8.3.5 Elbasvir/Grazoprevir

Elbasvir (EBR), an NS5A inhibitor, and grazoprevir (GZR), an NS3/4A protease inhibitor, have demonstrated high in vitro potency against HCV GT4 replicons, as well as resistance-associated substitutions (RASs) that confer resistance to first-generation protease inhibitors and RASs related to treatment failures on daclatasvir and ledipasvir [12].

In a pooled analysis of clinical trial data, a 12-week regimen of EBR/GZR was highly effective among treatment-naive (TN) participants with HCV GT4 infection [13] (Fig. 8.2). Recent EASL guidelines recommend EBR/GZR for 8 weeks in HCV GT1b patients who are TN and F0-F2. A study performed in France evaluated an 8-week regimen of EBR/GZR in participants with GT4 infection [14]. High rates of SVR were reported among treatment-naive participants with mild to moderate (F0–



	Treatment-naive participants with HCV GT4 infection
Virologic failure	2

*modified full analysis set population excludes 2 participants who discontinued treatment for reasons unrelated to study medication

Fig. 8.5 Elbasvir/grazoprevir regimen approved in HCV GT4 infected patients (a pooled analysis of participants with HCV GT4 Infection) reference: Asselah T et al. Liver Int. 2018

F2) fibrosis who have completed FW12 with a favorable safety profile (Fig 8.5) [14]. (Fig. 8.5).

8.4 Conclusion: A Long Way to HCV Elimination

HCV-GT4 infection constitutes almost 15% of all HCV infections globally and is the predominant infection in the Middle East and sub-Saharan Africa. Excellent efficacy and safety data regarding new direct-acting antivirals are now available, which make global elimination of HCV achievable.

HCV cure has a positive impact by improving survival, decreasing the incidence of cirrhosis and hepatocellular carcinoma [15]. Staging of disease either clinically or by laboratory analysis or radiologic approaches remains mandatory for HCV management. Patients with advanced cirrhosis will require continued care despite viral cure. The risk of HCC in patients with cirrhosis is reduced but not eliminated; patients treated with DAAs should continue to be closely monitored for HCC (ultrasound every 6 months). HCV cure has also a positive impact by improving overall quality of life for patients with HCV [16].

We must continue to be active and engaged in our respective countries with increasing screening and linkage to care for all patients.

Guidelines will help the physicians to manage patients. AASLD/IDSA and EASL guidelines for HCV GT4, HCV GT5, and HCV GT6 are proposed in Table 8.1 for

Table 8.1 Recommendations for HCV-GT4 treatment naive (EASL, AASLD/IDSA)Pts with GT4, 5, 6 HCV

HCV GT4	Compensated Cirrhosis
	▪ SOF/VEL 12 wks ▪ GLE/PIB 8 wks ▪ EBR/GZR 12 wks ▪ LDV/SOF 12 wks

Table 8.2 AASLD/IDSA HCV guidance for stage 4 or 5 chronic kidney disease

- Stage 4 (severe) CKD: eGFR 15-29 mL/min
- Stage 5 (end-stage) CKD: eGFR <15 mL/min

HCV GT	Recommended Regimens for Stage 4 or 5 CKD
1, 2, 3, 4, 5, 6	▪ GLE/PIB 8-16 wks*

*Use durations recommended for pts without CKD - based on cirrhosis, previous treatment experience.

HCV GT4-naive patients, which constitute the majority of patients [17, 18]. Regarding patients with chronic kidney disease, Table 8.2 provides AASLD/IDSA HCV guidance for stage 4 or 5 chronic kidney disease [19, 20].

Conflict of Interests T. Asselah has been a clinical investigator/speaker/consultant for AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche.

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Current Management of Patients with HCV Genotype 5 or 6

9

Geoffrey Dusheiko

9.1 Introduction

The hepatitis C virus (HCV), first characterised in 1989, is an enveloped virus with a 9.6 kb single-stranded RNA genome; the virus is classified within the genus *Hepacivirus* and is a member of the Flaviviridae family [1]. Recombinant DNA technological analysis of pools of plasma known to contain a relatively high titre of the putative agent finally enabled the molecular cloning and discovery of the genome of hepatitis C virus [2]. The RNA genome comprises approximately 9400 nucleotides of positive-sense RNA, comprising one long open reading frame encoding a polyprotein of 3010–3033 amino acids which is cleaved into functionally distinct polypeptides during or after translation. The RNA genome is subsequently translated into structural and non-structural proteins. The development of a subgenomic HCV RNA replicon capable of replication in the human hepatoma cell line, Huh 7, has been a major step in improving our understanding of HCV replication and importantly has allowed testing and evaluation of direct-acting antivirals (DAAs) [3–5].

The diagnosis of hepatitis C infection is made by measurement of anti- HCV by enzyme-linked immunosorbent assay (EIA), chemiluminescence assays or rapid diagnostic tests.

A positive antibody does not establish that an individual has active infection. The presence of HCV RNA establishes the definitive diagnosis of viremia and, if persistent, chronic HCV infection.

Population prevalence data are not adequately documented for many countries. However, it is widely thought that 2–3% of the world's population is chronically infected with HCV. Globally, perhaps 70 million individuals are chronically infected

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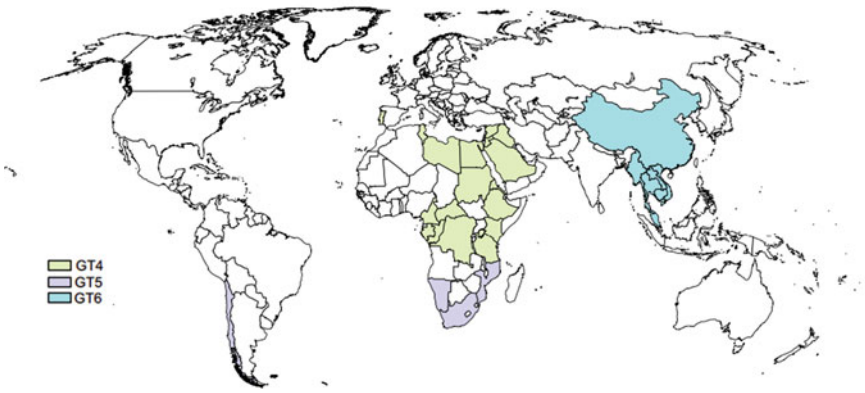

Fig. 9.1 Distribution of HCV genotype 4, 5, and 6 worldwide

and are at risk of cirrhosis or hepatocellular carcinoma (HCC) [6, 7]. Variation in the genome sequence of HCV isolates has enabled classification into types and subtypes. HCV comprises six major genotypes [8]. Current diagnostic tests detect all known genotypes of HCV. There are important geographical differences in prevalence and in the distribution of HCV genotypes [9]. Genotype 5 was thought to be confined to South Africa, but isolates of genotype infection have been identified in France, Spain, Syria and Belgium [10]. Type 6 is prevalent in Southeast Asia, Asian Americans and Asian Australians [11, 12] (Fig. 9.1).

The response to IFN as well as initial DAA combination treatment is affected by the host genotype, but combination DAAs with pan-genotypic activity are now available. Drug development has focused first on HCV genotype 1 infection; the initial trials did not incorporate large number of patients with genotypes 5 and 6, but evidence of efficacy has accumulated.

9.2 HCV Genotype 5

HCV genotype 5 is relatively highly conserved; one subtype, 5a, has been identified [13, 14]. HCV genotype 5 accounts for approximately 1·4 million cases of HCV infection worldwide; the majority of cases (>80%) of cases occur in southern and eastern sub-Saharan Africa. Genotype 5 was first reported from South Africa. An analysis of blood donors and the general population in South Africa revealed that overall genotype 5 is a relatively prevalent genotype in the region accounting for 54% of HCV cases in Black South Africans. HCV genotype 5 has also unexpectedly been reported in some regions of Belgium, France, Spain, Greece, the Netherlands and Luxembourg and Syria. These pockets of genotype 5 in Europe have been encountered in individuals who have had little connection with people from other countries, although that the networks of transmission have not been explained in most cases [15–17].

9.3 HCV Genotype 6

Genotype 6 is genetically diverse, and 23 subtypes have been described to date [3]. HCV genotype 6 represents about 1% of the total burden of HCV infection globally. Genotype 6 is found predominantly in Southeast Asia and Southern China, i.e. in countries such as Vietnam, Cambodia, Laos, Myanmar and Thailand. The proportion of HCV accounted for by type 6 in these countries ranges from 20 to >50% [11]. Specific assays, for example, Abbott GT II, PLUS assay and 5′ untranslated region sequencing, can differentiate genotype 6 from genotype 1 and avoid underestimation of genotype 6: an unexpected high prevalence of genotype 6 (18%) has been found in Taiwan. The majority were genotype 6 g, which is closely related to Indonesian strains [18].

9.4 Management of Genotype 5 and 6

The natural history and results of treatment of genotype 5 and 6 are less well characterised. However, there is no definitive evidence that infection with these genotypes is benign.

There are reports which have suggested that patients with genotype 5 HCV, in some regions, are older than are those with other genotypes which have high viral loads and a higher prevalence of cirrhosis [19]. Long-term infection with hepatitis C genotype 6 confers a similar risk of cirrhosis and HCC as does genotype 1 HCV infection [20].

9.5 Treatment of Chronic Genotype 5 and 6 Infection

There has been a pendulum shift away from alpha interferon and ribavirin treatment of chronic hepatitis C as DAAs are more efficacious and safer and overcome the previous constraints of IFN treatment. All patients irrespective of the degree of hepatic fibrosis are potential candidates for treatment. Fortunately IFN-free DAAs can be used in all patients, notably including those with decompensated cirrhosis, psychiatric illnesses, coexistent autoimmune illnesses, advanced renal disease, HIV coinfection or recurrence of hepatitis C post-liver transplantation. In many countries, hitherto the high cost of DAAs has restricted the use of these drugs to patients with advanced liver disease; however prioritisation has diminished as costs declined.

The goal of therapy is to eliminate HCV, as assessed by a sustained virological response (SVR) which is defined as undetectable HCV RNA in serum or plasma 12 weeks after completion of treatment. An SVR is associated with diminished hepatic necro- inflammation and fibrosis and a decline in liver-related as well as overall all-cause mortality [21, 22]. The risk of a viral relapse is low (1–5%).

Several new DAAs have been approved for the treatment of hepatitis C. These drugs can be classified as NS3 protease inhibitors, NS5A inhibitors and NS5B polymerase (nucleoside and non-nucleoside inhibitors). IFN-free DAA regimens

involve a combination of two to three DAAs with or without RBV. Recently approved regimens result in SVR rates of >95% in most patients after 8–24 weeks of treatment with the vast majority requiring only 12 weeks or less of treatment, without the necessity for ribavirin (Table 9.1).

The potential for drug-drug interactions must be examined in every patient undergoing treatment with DAAs. Evaluation requires a complete drug history prior to starting therapy and before starting concomitant medications during DAA treatment. A key web resource is *www.hep-druginteractions.org* whose recommendations are regularly updated.

National society guidelines provide a wealth of information, including those of AASLD (Recommendations for Testing, Managing, and Treating Hepatitis C http://www.hcvguidelines.org accessed December 2016) and EASL [23].

The introduction of DAAs for HCV has transformed the outcome for all genotypes including genotype 5 and 6; the more recent development of pan-genotypic treatments may soon obviate the need for genotyping.

9.6 Direct-Acting Antivirals for HCV GT5 Infection

Although the number of patients with genotype 5 treated in clinical trials has been limited, current (2020) [24] option would include one of three regimens: the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) (in a single tablet given once daily); the fixed-dose combination of glecaprevir (300 mg) and pibrentasvir (120 mg) (in three tablets each containing 100 mg of glecaprevir and 40 mg of pibrentasvir, given once per day with food); or the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet given once per day [25–28].

The use of protease inhibitors is not recommended in patients with Childs B or C cirrhosis. The timing of treatment, before or after liver transplantation in patients who are candidates for a liver transplantation, requires consideration. Patients with decompensated cirrhosis, awaiting liver transplantation with a MELD score of <18–20, may be prioritised for treatment prior to liver transplantation. Treatment for 12 weeks with sofosbuvir and ledipasvir, or sofosbuvir and velpatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 or ≥ 75 kg, respectively) is recommended. If ribavirin cannot be tolerated, treatment can be extended to 24 weeks. All patients with post-transplant recurrence of HCV infection should be considered for therapy as soon as the patient has stabilised.

The combination of sofosbuvir-velpatasvir-voxilaprevir could be reserved for salvage or rescue treatment [29]. In low-income countries, generic sofosbuvir (400 mg) and daclatasvir (60 mg) can be considered to scale up treatment rates. Theoretically, based on results in other genotypes, adolescents >12 years or weighing >35 kg could be treated with sofosbuvir and ledipasvir. Paediatric studies are in progress.

Table 9.1 Current treatment options for genotypes 5 or 6 IFN treatment naive or experienced with or without cirrhosis

Genotype	TN or TE	SOF LDV	SOF VEL	SOF DCV	GLE PIB	SOF VEL VOX
Patients without cirrhosis						
5 or 6	TN	12 weeks	12 weeks	12 weeks	8 weeks	8 weeks
	TE	12 weeks		12 weeks	8 weeks	12 weeks
Patients with cirrhosis						
5 or 6	TN	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
	TE	12 weeks + RBV		12 weeks + RBV	12 weeks	12 weeks

TN treatment naive, *TE* treatment experienced, *LDV* ledipasvir, *SOF* sofosbuvir, *VEL* velpatasvir, *DCV* daclatasvir, *GLE* glecaprevir, *PIB* pibrentasvir, *VOX* voxilaprevir, *RBV* ribavirin

9.7 Sofosbuvir-Velpatasvir

Treatment-naive and experienced patients (i.e. previously treated with pegylated interferon and ribavirin) without cirrhosis, or with compensated cirrhosis, with genotype 5 infection, can be treated with the combination of sofosbuvir and velpatasvir for 12 weeks.

In the ASTRAL-1 trial, participants infected with genotype 5 were not randomised but were assigned solely to the sofosbuvir-velpatasvir group [8]. An SVR was observed in 97% (34/35); 14% had cirrhosis, 69% were treatment-naive, and 31% were treatment-experienced. Among the treatment-naive patients treated with sofosbuvir plus velpatasvir, 23 (96%) of 24 with genotype 5 infection achieved a SVR. Among the treatment-experienced cohort, 11 (100%) of 11 with genotype 5 infection achieved an SVR [30].

9.8 Glecaprevir-Pibrentasvir

Treatment-naive and treatment-experienced patients with HCV genotype 5 without cirrhosis can be treated with glecaprevir and pibrentasvir for 8 weeks. However, patients with cirrhosis should be given the same regimen for 12 weeks. Treatment with glecaprevir and pibrentasvir is not recommended for patients with decompensated cirrhosis.

The efficacy of 8-week glecaprevir-pibrentasvir treatment and 12-week treatment in non-cirrhotic patients with genotype 5 or 6 infection has been analysed (Surveyor-II, Part 4 and Endurance-4). Although the numbers were small, SVRs were reported in 100% [31].

9.9 Sofosbuvir and Ledipasvir

Sofosbuvir-ledipasvir can be considered for treatment-naive patients infected with HCV genotype 5 without cirrhosis or with cirrhosis; patients should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks. The evidence for this was obtained in a phase II trial, in which 41 treatment-naive and treatment-experienced patients infected with HCV genotype 5, including 9 with compensated cirrhosis, were treated with sofosbuvir and ledipasvir without ribavirin for 12 weeks: 95% (39/41) achieved a SVR.

Twenty of 21 (95%) treatment-naive patients achieved a SVR. Nineteen of 20 (95%) treatment-experienced patients achieved a SVR. Ten of the patients with compensated cirrhosis achieved a SVR [13, 32].

9.10 Sofosbuvir-Velpatasvir-Voxilaprevir

In the POLARIS-2 trial, 94% of 18 treatment-naive or treatment-experienced patients with genotype 5 infection responded to 8-week duration; no patients were treated in the 12-week arm duration [33].

9.11 Direct-Acting Antivirals for HCV-GT6 Infection

The same three primary treatment options are available for those with HCV genotype 6 as for genotype 5. However, the number of patients treated in trials has been limited [25].

9.12 Sofosbuvir-Velpatasvir

Treatment-naive or treatment-experienced patients infected with HCV genotype 6, without cirrhosis or with compensated cirrhosis can be treated with sofosbuvir and velpatasvir for 12 weeks. In the phase 3 ASTRAL-1 trial, 100% of 38 treatment-naive patients achieved a SVR. 3/3 treatment-experienced patients achieved a SVR [34].

9.13 Glecaprevir-Pibrentasvir

Treatment-naive and treatment-experienced patients with HCV genotype 6 without cirrhosis can be treated with glecaprevir and pibrentasvir for 8 weeks. Patients with Child-Pugh A cirrhosis should be treated for 12 weeks with this combination. Treatment for patients with decompensated cirrhosis with the regimen is not recommended.

This evidence is based on the results of the phase 2 SURVEYOR-2 trial in which a SVR rate of 90% (9/10) occurred in treatment-naive and treatment-experienced patients without cirrhosis, treated with glecaprevir and pibrentasvir for 8 weeks [35]. In ENDURANCE-4, a SVR was observed in 100% (19/19) in patients without cirrhosis treated for 12 weeks [31]. In EXPEDITION-1, 7/7 (100%) of patients with cirrhosis achieved a SVR [36].

Although the numbers were small, 100% of patients with genotype 6 and HIV coinfection without cirrhosis responded to 8 weeks of treatment [37].

9.14 Sofosbuvir-Ledipasvir

Treatment-naive patients infected with HCV genotype 6 without cirrhosis or with compensated cirrhosis can be treated with the combination of sofosbuvir and ledipasvir for 12 weeks. In an open-label, phase 2 study from New Zealand, treatment-naive and treatment-experienced patients with genotypes 3 or 6 HCV infection were enrolled. 24/25 patients with genotype 6 who received ledispasvir-sofosbuvir for 12 weeks achieved a SVR [38]. A real-world effectiveness study in Taiwan has also confirmed high (97%) SVR rates in Taiwanese patients with genotype 6 [14].

9.15 Sofosbuvir-Velpatasvir-Voxilaprevir

SOF VEL VOX can be considered for management of resistance based on results observed in the POLARIS-2 study [29]. Thirty of 30 (100%) achieved an SVR after 8-week duration; a similar response was observed in nine patients treated for 12 weeks [33].

9.16 Further Management

The risk of HCC in patients with cirrhosis is reduced after SVR, but by no means eliminated; patients with cirrhosis or advanced HCC treated with DAAs should be closely monitored for HCC by a combination of ultrasound and alpha fetoprotein testing every 6 months [39].

Programmes to eliminate HCV must include increased screening (either risk based or universal), linkage to care as well as increased access to treatment worldwide. Reducing the cost and increasing access to rapid point of care diagnostic tests will be crucial to meet elimination targets. DAA cost will also be critical. Generic use is widespread in many countries listed as access countries [40]. A recognition of the disease burden posed by hepatitis C, governments and policy-makers, and the political will to increase treatment rates in low-, middle- and high-income countries, is required. Patients with genotype 5 or 6 who failed previous treatment and developed resistance-associated variants (RAV) to NS5A should be rescued with future appropriate combinations [29, 41].

Achievement of HCV elimination will require concerted national policies for screening and testing, combined with affordable drug costs, negotiated discounts and appropriate budgeting to expedite unrestricted access to treatment; the costs of implementing widespread treatment are high. In low-income countries, approved generic DAAs are often used; however, patients frequently must meet the costs of treatment out of pocket [42, 43].

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Management of Patients with Acute Hepatitis C

10

Markus Cornberg

10.1 Epidemiology, Natural Course, and Diagnosis of Acute HCV Infection

Wordwide 64–103 million people are chronically infected with the hepatitis C virus [1]. Transmission of HCV occurs mainly via contaminated blood. In Western countries, the majority of new acute HCV infections occur among people who inject drugs (PWID), especially in the prison setting [2, 3]. However, sexual transmission with risk behavior under the influence of drugs (chemsex) has increased in recent years [4]. Tattooing or acupuncture with non-sterile equipment, occupational exposure, i.e., needlestick injuries and contact with blood from an infected person are other risk factors [5, 6]. In developing countries with poor infection control measures, invasive medical procedures, i.e., dental care, surgery, or blood transfusion are still a major risk for HCV transmission [7, 8]. The real number of acute HCV infections is very difficult to determine because of the generally asymptomatic course of the infection [9]. There are, at the most, 20% of patients who develop jaundice and fulminant hepatitis C is a rare event documented in few case reports [10–12].

10.1.1 Diagnosis of Acute HCV Infection

The screening of acute HCV infection requires not only HCV antibody (anti-HCV) but also HCV RNA testing because anti-HCV can be negative during a window

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period of 4–6 weeks after infection or even longer [13]. An alternative screening method for acute HCV infection at lower costs is HCV core antigen (HCV cAg). The sensitivity and specificity of HCV cAg during acute hepatitis C is around 80–90% and 100%, respectively [14, 15].

10.1.2 Definition of Acute HCV Infection

Acute hepatitis C is usually defined as infection within the first 6 months after HCV acquisition. However, the exact classification of an acute HCV infection is often challenging and a definite test to determine acute HCV infection does not exist.

The best indicator for an acute HCV infection is the detection of HCV RNA without anti-HCV antibody or a documented anti-HCV seroconversion. However, patients with immunosuppression or patients on hemodialysis may have false-negative HCV antibody test results during a chronic HCV infection [16–18]. Elevation of ALT >10-times ULN and or jaundice are strong indicators for acute hepatitis. However, flares of chronic hepatitis C have been described, especially for patients with genotype 2 [19] and further other infections such as acute hepatitis A or hepatitis E need to be excluded. Patients during acute hepatitis A may even clear chronic HCV [20]. Therefore, also patients with chronic HCV infections may be misclassified as acute resolving infections. In addition, the exact point-of-time of infection is not easy to determine in most cases because the mode of acquisition is often unknown or multiple events have occurred in patients with high-risk behavior. Consequently, studies investigating patients with acute HCV infection are very often heterogeneous in terms of case definition [21]. In many studies, patients have been classified as early or recent acute HCV infection rather than acute HCV infection because the time after potential exposure was longer than six months.

10.1.2.1 Prediction of Spontaneous Clearance

Spontaneous clearance of HCV occurs in 10–50% of patients while 50–90% of cases develop chronic hepatitis C with the risk of progress to liver cirrhosis. Spontaneous clearance occurs by definition within six months after infection. Importantly, a single HCV RNA measurement during acute HCV infection is not sufficient to determine the sustained clearance of HCV. Transient HCV RNA suppression and fluctuations of HCV RNA in the first weeks after infection can occur [22].

Many research studies have been performed to identify viral or host marker, which might predict spontaneous clearance of HCV infection. At the front, there is not a single marker that can 100% foresee spontaneous clearance. A key factor that determines the chance of spontaneous clearance is the host immune response. Broad and multi-specific immune responses are associated with viral clearance whereas immune evasion or T cell exhaustion leads to chronicity [23, 24]. However, the analysis of cellular immune responses is not useful for routine praxis. Host genetic determinants associated with the immune system or soluble immune marker may provide a better diagnostic tool. In fact, polymorphisms in human leukocyte antigens (HLA), interferon-stimulated genes, killer immunoglobulin-like receptors, and

chemokines such as IP-10 have been correlated with spontaneous clearance of HCV [25–28]. Probably the strongest genetic association with viral clearance during acute or recent HCV infection exists with polymorphisms upstream of IL28B, which encodes for interferon lambda 3 [28–32].

Other factors associated with spontaneous clearance of HCV and easier to record are female gender and symptomatic acute hepatitis C [32, 33]. Interestingly, one study observed that abstention from alcohol may increase the likelihood of spontaneous clearance among women [34].

Also, viral factors such as genotype 1 and rapid HCV RNA elimination within four weeks after onset of symptoms are associated with spontaneous clearance [35, 36]. Combining different factors in a score may increase the predictive value for spontaneous clearance [37].

10.1.2.2 Prevention of HCV Infection

Because of the high risk of >50% to develop chronic hepatitis C after HCV infection, there is a high unmet need for prevention measures. In contrast to hepatitis B, there is no prophylactic vaccine for HCV infection. The development of such a vaccine is challenging due to the high variability of the virus and immune escape mechanisms [38]. Although the design of a prophylactic vaccine is difficult and chronic hepatitis C can meanwhile be successfully treated with direct-acting antivirals (DAA), some researchers still believe in the need for a vaccine and a first trial in humans at risk is underway [39]. For now, prevention measures are limited to hygiene, testing blood products, and needle and syringe exchange programs [2, 40]. However, also other injection equipment such as filters and water containers have to be considered as well, as HCV stability in water can last for up to three weeks [41].

In case of a health care-related needlestick injury (NSI), the possibility to acquire HCV ranges from 0.1 to 3% depending on the injury and the viral load of the source patient [42–44]. It is estimated that more than 600,000 occupational NSIs occur annually in the United States. Thus, the topic of HCV prevention is relevant in occupational medicine.

10.2 Management of Acute HCV Infection

The high rate of progression to chronic hepatitis C and the absence of a vaccine or postexposure prophylaxis is the motivation to discuss early treatment of acute HCV infection. In the interferon era, an additional argument for an early treatment was the higher response with shorter treatment duration compared with the troublesome and rather ineffective therapy with interferon alfa (IFN) plus ribavirin of chronic hepatitis C [45]. However, early treatment of acute HCV infection is unnecessary for those who clear the virus spontaneously. Another option is the treatment of only those patients who remain HCV RNA positive for a longer time, i.e., for more than 3 months after the onset of symptoms [46].

10.2.1 Treatment of Acute HCV Infection with Interferon Alfa

Several studies have investigated the effect of early treatment with IFN or pegylated IFN (PEG-IFN) monotherapy in patients with acute HCV infection (Table 10.1). The study results suggest that 24 weeks of therapy prevents chronic hepatitis C in 71–98% of patients with acute HCV infection. The strategy to wait for more than 3 months after the onset of symptoms and treat those who remained HCV RNA

Table 10.1 Pivotal studies with interferon alfa in acute or recent HCV monoinfection

Study and population	Treatment	Outcome
Vogel et al. [47] N = 24, age 32 years, 79% PWID, GT1, 3 and mixed GT	10 MU IFN2b daily until normal ALT (18–43 days)	22 patients completed therapy 18 patients with SVR
Jaeckel et al. [48] N = 44, 43% male, 20% PWID, age 36 years, time from evidence of infection 89 days	4 weeks 5 MU IFN2b daily, 20 weeks 5 MU IFN2b tiw	43/44 (98%) SVR, 1/44 relapse
Santantonio et al. [49] N = 16, time after the onset of symptoms 12 weeks	24 weeks 1.5 μg/kg PEG-IFN2b	15/16 (94%) SVR
Wiegand et al. [50] N = 89 Time from evidence of infection 76 days	24 weeks 1.5 μg/kg PEG-IFN2b	71% SVR, 89% SVR in adherent patients
Broers et al. [51] N = 27 acute and recent HCV (<12 months from infection), 81% PWID	24 weeks 1.5 μg/kg PEG-IFN2b	6/22 refused therapy, 2/22 lost-to FU 8/14 (57%) SVR, 6/14 stopped due to side effects (1 with SVR), 8/14 with adherence (7 with SVR)
Deterding et al. [52] N = 107 symptomatic (randomized 1:1) N = 25 asymptomatic	**Symptomatic (a)** 24 weeks 1.5 μg/kg PEG-IFN2b **Symptomatic (b)** delayed 24 weeks 1.5 μg/kg PEG-IFN2b + RBV **Asymptomatic (c)** 24 weeks 1.5 μg/kg PEG-IFN2b	(a) 37/55 SVR (67%) (b) 28/52 SVR (54%) 11/52 (21%) spontaneous clearance 22/52 (42%) lost-to FU (c) 18/25 (72%) SVR
Santantonio et al. [53] N = 130, not spontaneously resolved by week 12 after onset	(N = 44) 24 weeks 1.5 μg/kg PEG-IFN2b (N = 43) 12 weeks 1.5 μg/kg PEG-IFN2b (N = 43) 12 weeks 1.5 μg/kg PEG-IFN2b + RBV	31/44 (71%) SVR, PP 82% SVR 31/43 (72%) SVR, PP 82% SVR 31/43 (72%) SVR, PP 82% SVR

People who inject drugs (PWID), Ribavirin (RBV), Pegylated interferon alfa (PEG-IFN), Intention-to-treat analysis (ITT), Per-protocol analysis (PP), Sustained virological response (SVR), Follow-up (FU)

Table 10.2 Pivotal Studies with interferon alfa in acute or recent HCV infection in HIV patients

Study and population	Treatment	Outcome
Vogel et al. [55] N = 111, 100% male, 64% GT1	N = 14 PEG-IFN N = 97 PEG-IFN + RBV 24–48 weeks, median duration 25 weeks	62% SVR, no difference in SVR by genotype, CD4(+) T-cell count, HIV RNA, HCV RNA, or use of ribavirin
Dore et al. [54] N = 167, 79% drug use in previous 6 months, N = 111 treated (n = 35 with HIV)	N = 74 PEG-IFN2a 24 weeks N = 35 PEG-IFN2a + RBV 24 weeks	55% SVR (ITT), PP 72% SVR 74% SVR (ITT), PP 75% SVR Decreased social functioning and current opiates associated with lower SVR
Boesecke et al. [56] N = 34 GT1, 100% male MSM, 40 yrs	N = 19 PEG-IFN + RBV + telaprevir 12–24 weeks N = 15 PEG-IFN + RBV 24–48 weeks	15/19 (80%) SVR Additional side effects of PI 12/15 (80%) SVR
Fierer et al. [57] N = 67 GT1, 100% male	N = 19 PEG-IFN + RBV + telaprevir 12 weeks N = 48 PEG-IFN + RBV 24–72 weeks	16/19 (84%) SVR 30/48 (63%) SVR
Hullegie et al. [58] N = 57 GT1, within 26 weeks after infection	PEG-IFN + RBV + boceprevir 12 weeks PEG-IFN + RBV 24 weeks (historical control, n = 73)	86% SVR (ITT) 100% SVR if RVR4 5/5 (100%) SVR if treated within 12 weeks after infection 84% SVR

Protease inhibitor (PI), Ribavirin (RBV), Pegylated interferon alfa (PEG-IFN), Intention-to-treat analysis (ITT), Per-protocol analysis (PP), Sustained virological response (SVR)

positive with PEG-IFN with or without ribavirin can also be effective in more than 90% [46, 49, 53]. However, adherence to therapy is fundamental for both scenarios. Patients with acute HCV infection may have some issues with compliance, especially if patients take drugs and are not on a stable opiate substitution therapy or have no social support [51, 54].

Lost to follow-up rates were high in several studies that resulted in much lower intention-to-treat response rates (Tables 10.1 and 10.2). However, a wait-and-see strategy was associated with a higher dropout rate compared with immediate treatment in a randomized study [52]. Thus, immediate treatment seems preferable in populations where loss to follow-up is an important issue.

Immediate treatment with IFN was also recommended as preferred option for patients with unfavorable factors associated with spontaneous clearance (asymptomatic patients, unfavorable IL-28B genotype) [30].

Most studies that investigated the treatment of acute HCV infection were performed in HIV coinfected patients. The results suggest a potential benefit for PEG-IFN and ribavirin combination therapy in maximizing virological responses (Table 10.2). However, many patients were rather late acute or recent HCV infections than early acute infections. In fact, ribavirin was important particularly

in those patients with a longer duration of HCV infection and unfavorable IL28B genotypes [59].

There are also data for the treatment of acute HCV infection with PEG-IFN, Ribavirin plus a first-generation protease inhibitor (Table 10.2). These data confirm high response rates in HIV coinfected patients with acute HCV infection. Interestingly, the response rate was 100% in patients that received PEG-IFN, ribavirin, and boceprevir treatment within 12 weeks after infection compared to 85% who have been treated later [58]. However, triple therapies should not be used anymore due to additional side effects of the first-generation protease inhibitors [56].

10.2.2 Treatment of Acute HCV Infection with IFN-Free Regimens

As IFN-free combination therapies with direct-acting antivirals (DAA) have shown cure rates of more than 95% in patients with chronic HCV infection, the discussion about early IFN-based therapy in acute or recent HCV infection seems to be outdated, at least in countries where DAA are available. Thus, waiting until the HCV infection becomes chronic has no more disadvantage and is recommended by the latest AASLD guidelines (www.hcvguidelines.org). Nevertheless, early treatment of acute HCV infection may still be an important instrument in certain situations, i.e., to prevent transmission in high-risk groups. Additionally, treatment duration may even be cut down to less than 8 weeks. The first trials investigating short-term DAA therapies in patients with acute HCV infection have been published. Several studies investigated sofosbuvir plus ribavirin, which can meanwhile be regarded as suboptimal treatment in chronic hepatitis C as well as in acute or recent HCV infection (Table 10.3). Short-term therapy of acute or recent HCV infection with two potent DAA, i.e., sofosbuvir plus an NS5A inhibitor achieve cure rates similar to aforementioned rates with IFN-based treatment, but with shorter treatment duration and more favorable safety profile. Two studies investigated 6 weeks of sofosbuvir/ledipasvir in patients with acute HCV genotype 1 or 4 infection [63, 64]. All 20 patients with acute HCV monoinfection achieved SVR, while 3 out of 26 HIV coinfected patients experienced a virological relapse (Table 10.3). High baseline HCV RNA was associated with treatment failure in HIV coinfected patients [63]. Despite the limited data available, the current practice guidelines of the European Association for the Study of the Liver (EASL) recommend that patients with acute HCV infection should be treated with a combination of sofosbuvir and an NS5A inhibitor for 8 weeks [65]. However, the ideal DAA combination and treatment duration is not known for infections with other genotypes, especially genotypes 2 and 3. In this case sofosbuvir/velpatasvir should be preferred or alternatively glecaprevir/pibrentasvir that are pangenotypic DAA fixed-dose combinations. However, it is unknown if sofosbuvir/velpatasvir is as effective when given for a short duration of less than 12 weeks. For glecaprevir/pibrentasvir there might be safety concerns using a protease inhibitor in case of a severe symptomatic acute hepatitis C with liver impairment.

Table 10.3 Pivotal Studies with IFN free DAA therapy in acute or recent HCV infection with or without HIV coinfection

Study and population	Treatment	Outcome
Martinello et al. [60] N = 19 (recent HCV infection), 89% male, 84% IDU, 74% HIV, 68% GT-1a, median duration of infection 37 weeks	6 weeks SOF + RBV	6/19 (32%) SVR, 9/19 relapse, 2/19 nonresponse, 1/19 reinfection, 1/19 lost to FU
El Sayed et al. [61] N = 12 (early HCV infection)	12 weeks SOF + RBV	11/12 (92%) SVR, 1 relapse (more characteristic of chronic than of early HCV infection)
Naggie et al. [62] N = 17, 88% GT-1, age 45 yrs, median time from evidence of infection 140 days	12 weeks SOF + RBV	10/17 (50%) SVR, 7/17 (41%) relapse
Rockstroh et al. [63] N = 26, 100% male, 73% GT-1a, 27% GT-4, CD4 >500	6 weeks SOF/LDV	20/26 (77%) SVR (79% GT-1, 71% GT-4), 3/26 relapse, 2/26 lost-to FU, 1/26 re-infection
Deterding et al. [64] N = 20, 55% GT-1a, 45% GT-1b, time from diagnosis to therapy 32.8 days	6 weeks SOF/LDV	20/20 (100%) SVR

Sofosbuvir (SOF), Ledipasvir (LDV), Ribavirin (RBV), Sustained virological response (SVR), Follow-up (FU)

10.3 Reinfection after Treatment of Acute HCV Infection

Elimination of HCV with DAA does not lead to sterilizing immunity and reinfection either after spontaneous HCV clearance or after successful DAA therapy can occur in individuals with ongoing risk behavior. A study from Australia and New Zealand reported 10 cases of HCV reinfection out of 120 individuals who have been treated for recent HCV infection after a median follow up of 1.08 years (incidence 7.4/100 person-years). Reinfection incidence was higher in persons with active drug use at the end of treatment [66]. A quite similar high incidence of reinfection (7.3/100 person-years) after spontaneous HCV clearance or SVR after antiviral treatment was reported in HIV-positive men who have sex with men [67]. The incidence of HCV reinfection can even be as high as 12.3/100 person-years and multiple reinfections are possible [68]. This emphasizes the need for additional prevention measures beyond antiviral therapy in at-risk populations, which includes continued posttreatment surveillance, harm-reduction concepts and education. For example, opioid substitution therapy and mental health counseling could reduce HCV reinfection risk among PWID [69].

10.4 Prevention of HCV Infection by Preemptive DAA Therapy

The high success of short-term pangenotypic DAA therapy in acute or early HCV infection will consequently lead to discussions considering preexposure or postexposure prophylaxis (PREP or PEP) for HCV, which is commonly and effectively used to prevent HIV infection [70]. So far there are no data on the efficacy or cost-effectiveness of PREP or PEP to prevent HCV infection, i.e., after occupational exposure. However, the effective DAA therapy may open opportunities to use HCV infected donor organs for transplantation. In a recent study, patients undergoing dialysis and who had long anticipated waiting times for a kidney transplant were offered to receive an HCV-infected kidney. Per protocol, 10 patients received HCV-infected kidneys. All patients were tested positive for HCV three days after transplantation. All patients received the DAA fixed-dose combination grazoprevir/elbasvir and achieved sustained virological response [71]. The pilot trial showed the proof-of-concept that transplantation of HCV infected organs into HCV-negative recipients, followed by DAA treatment, is possible.

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Management of Transplant Patients Infected with HCV

11

Bruno Roche, Audrey Coilly, and Didier Samuel

Abbreviations

ART	Antiretroviral therapy
BOC	Boceprevir
CH	Cholestatic hepatitis
CNI	Calcineurin inhibitors
CsA	Cyclosporine
CYP	Cytochrome
DAA	Direct-acting antiviral
DCV	Daclatasvir
DDI	Drug-to-drug interactions
EBR	Elbasvir
EPO	Erythropoietin
EVR	Early virological response
GLE	Glecaprevir
GZR	Grazoprevir
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LDV	Ledipasvir
LT	Liver transplantation
NA	Not available

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PEG-IFN	pegylated interferon
PI	Protease inhibitors
PIB	Pibrentasvir
RAS	Resistance-associated substitution
RBV	Ribavirin
RNA	Ribonucleic acid
RVR	Rapid virological response
SIM	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virological response
Tac	Tacrolimus
TVR	Telaprevir
VEL	Velpatatsvir
VOX	Voxilaprevir
2D	Paritaprevir/r, ombitasvir
3D	Paritaprevir/r, ombitasvir, dasabuvir

11.1 Introduction

Hepatitis C virus (HCV) infection is a leading cause of cirrhosis and hepatocellular carcinoma and one of the main indications for liver transplantation (LT) [1]. Historically, viral recurrence occurred in all patients with viral replication at the time of LT. Graft fibrosis progression rate was accelerated leading to cirrhosis in around 30% of untreated patients within 5 years. HCV graft infection was the cause of two-thirds of graft failure in these patients and was the most frequent cause of death [2, 3]. Viral eradication using antiviral therapy improves patient and graft survival [4–6]. Pegylated interferon (PEG-IFN)-ribavirin (RBV) and first-generation NS3/4 protease inhibitors (PI): boceprevir (BOC) or telaprevir (TVR) associated to PEG-IFN-RBV are no more used to treat HCV infection post-LT related to lower efficacy, poor tolerability, and drug–drug interactions (DDI) with immunosuppressive therapy [7–10]. Since 2013, the use of Sofosbuvir (SOF), a NS5B polymerase inhibitor, with RBV has led to improvements in tolerability and efficacy [11, 12]. Further improvement in SVR rates was observed using SOF in combination with a second direct-acting antiviral (DAA): Simeprevir (SIM), Ledipasvir (LDV), Daclatasvir (DCV), Elbasvir (EBR), and RBV, or the regimen of Ombitasvir, Paritaprevir/Ritonavir, Dasabuvir (3D), and RBV [13–28]. Limitations of these regimens are suboptimal efficacy in some subgroups of patients, none are pangenotypic, mostly contain RBV, and some have the potential for clinically significant DDIs. More recently, a new wave of pangenotypic, RBV-free, DAA regimens including SOF–Velpatasvir (VEL), Glecaprevir (GLE)–Pibrentasvir (PIB), and Voxaliprevir (VOX), were approved [29, 30]. These regimens maintain activity against most of the common resistance-associated substitutions (RAS) of HCV

genotypes 1–6 that are known to confer resistance to previously approved antiviral therapies.

Most patients are currently treated before LT. Thus, actually, the main indication for LT is hepatocellular carcinoma in cirrhotic patients after viral clearance. Overall, the use of new DAAs has many potential implications, such as reducing the need for LT in a proportion of patients, allowing that the majority of patients are transplanted with undetectable HCV RNA and improving graft and patient survival after LT. This review reports available data on the treatment of HCV infection by DAAs in the transplant setting and discusses new dilemmas and challenges.

11.1.1 Natural History of HCV Recurrence

Historically, viral recurrence was universal in patients with detectable serum HCV RNA at the time of transplantation. The course of HCV-related liver disease is accelerated in LT recipients leading to cirrhosis in 20 to 30% of patients within 5 years [2]. High HCV RNA levels in both serum and the liver during perioperative period, older donor age, black recipient race, steatosis of the graft, the IL28B genotype of the donor and the recipient, the degree and composition of the immunosuppressive regimen and HIV co-infection were associated with a higher fibrosis progression rate on the graft [2, 3, 31–34]. Patient and graft survival were decreased as compared with other indications for LT. Patients with HCV recurrence have a risk of graft failure in the early post-LT period related to cholestatic hepatitis (CH), observed in 2 to 10% of patients characterized by high viral load in the serum and extensive fibrosis on the graft [35]. Later in the course, graft cirrhosis may occur and then hepatocellular carcinoma. Actually, eradication of HCV infection before LT, using DAAs could eliminate the risk of HCV recurrence in the majority of patients [16, 18, 19, 36–41]. The second option is to treat HCV infection after LT with a combination of DAAs leading to HCV clearance in more than 90% of patients and improving patient and graft survival [11–28].

11.1.2 Management of HCV Recurrence

11.1.2.1 New Direct-Acting Antiviral Agents

Several classes of DAAs have reached the market and target different viral nonstructural proteins, including the NS3/4A protease, the NS5B polymerase, and the NS5A protein [42]. Their efficacy and barrier to resistance may depend on HCV genotype/subtype [43].

New wave NS3/4A PIs include GLE and VOX. Pharmacokinetic analysis of PIs in patients with cirrhosis showed higher exposure to the drug than in those without cirrhosis. The AUC of GLE is 33% higher in patients with Child-Pugh A cirrhosis, 100% higher in patients with Child-Pugh B cirrhosis and increased to 11-fold in those with Child-Pugh C cirrhosis [29, 30]. Exposure to VOX is 73% higher in patients with Child-Pugh A cirrhosis and the AUC is three- and fivefold higher in

patients with moderate and severe hepatic impairment, respectively [29, 30]. Thus, GLE and VOX should not be used in patients with Child-Pugh B or C cirrhosis.

Nucleos(t)ide analog NS5B polymerase inhibitors such as SOF are active against all genotypes and have a high potency and a high barrier to resistance. Indeed, the S282T mutation conferring resistance to this class dramatically impairs viral replication and has been rarely detected in patients failing SOF-based treatments.

NS5A inhibitors such as DCV, LDV, VEL, EBR, and ombitasvir are active against all genotypes and have a high potency and a low barrier to resistance. Mutations at positions 31 and/or 93 confer a broad cross-resistance to NS5A inhibitors. Unlike NS3 RASs, NS5A RASs selected during treatment are relatively fit in terms of replication capacity and might persist for a long period of time after treatment discontinuation [44, 45]. Newer NS5A, such as PIB, has a pangenotypic efficacy and a higher barrier to resistance. NS5A inhibitors plasma exposure is similar in patients with moderate and severe hepatic impairment.

Combination of DAAs, which target different steps of viral replication, should provide additive or synergistic antiviral potency and prevent the emergence of DAAs resistance [42]. The HCV drug combinations actually available are SOF-VEL, SOF-VEL-VOX, and GLE-PIB [29, 30].

11.1.2.2 Monitoring and Timing of the Initiation of Antiviral Therapy (Fig. 11.1)

The best strategy is to prevent recurrence by clearance of HCV infection before LT. Using new DAAs, it is expected that obtaining an SVR before LT is possible in the vast majority of patients and lead to some patients being removed from the waiting list [16, 18, 19, 36–41]. Results reported with prophylactic antiviral therapies using anti-HCV monoclonal antibodies or HCV entry inhibitors post-LT are limited [46]. After LT, two options are possible: Preemptive treatment, within one-month post-LT, before the occurrence of hepatitis on the graft, or for the majority of patients, treatment at the time of established chronic hepatitis.

11.1.2.3 Pretransplant Antiviral Therapy

The optimal strategy is to achieve SVR before LT using DAA-based pangenotypic regimens [29, 30]; in this case, there is no risk of HCV recurrence on the graft. Treatment of HCV infection in patients awaiting LT has two goals: preventing HCV reinfection after LT and stabilizing or improving liver function before LT. Patients with decompensated cirrhosis should be treated in experienced centers with access to LT and closely monitored to detect worsening of liver function during therapy. Several studies with DAAs combinations containing SOF and an NS5A inhibitor have demonstrated significant improvements in liver function in around one-third of patients [16, 18, 19, 38, 41, 47–49].

There are some limitations in pre-LT antiviral therapy: few data are available on the efficacy and safety of news DAAs regimens in decompensated cirrhosis (i.e., MELD score $>$ 18–20), which patients could improve and maybe delisted, the use of antiviral drugs, mainly SOF, is limited in patients with severely impaired kidney function (i.e., creatinine clearance $<$30 ml/min), more data are needed to understand

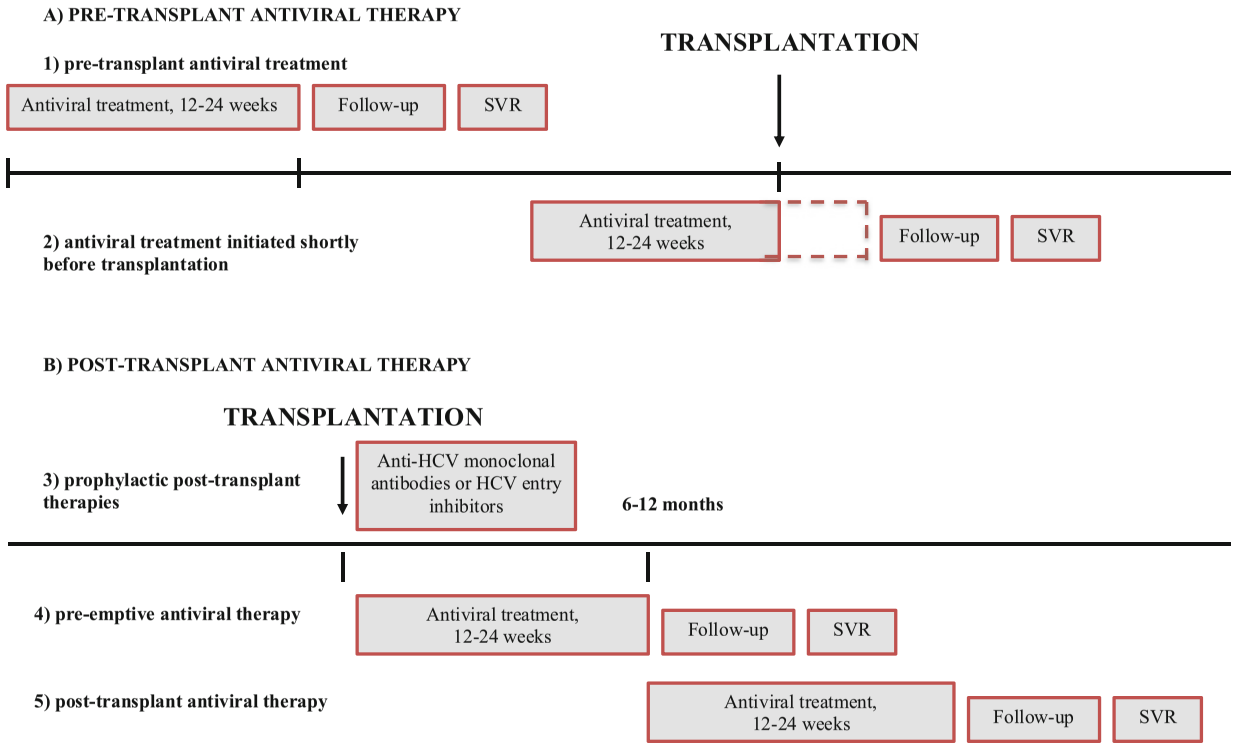

Fig. 11.1 Antiviral treatment modalities before or after liver transplantation. SVR: Sustained virological response

the consequences of virologic failure following DAA therapy as well as the development of effective strategies to treat these patients pre- or post-LT [16, 18, 19, 38, 41, 47–49]. Patients with MELD score > 20 or severe portal hypertension complications could be less likely to improve and might be better served by LT than antiviral treatment. Some studies showed that despite a high SVR rate, changes in MELD score and hepatic function tests in long-term follow-up are marginal [50]. If delisted, patients will keep cirrhosis with the risk of subsequent decompensation, HCC occurrence, and death. The use of protease inhibitors is contra-indicated in patients with decompensated cirrhosis because of higher drug exposure and risk of toxicity. Thus, the combination of SOF and VEL +/− RBV 12 to 24 weeks is the treatment of choice for patients with decompensated cirrhosis [29, 30]. It is relevant to choose the most effective antiviral combination to minimize the possibility of virological relapse and the selection of RASs because they could infect the graft and persist for prolonged time in the setting of immunosuppression.

A second strategy is to achieve on treatment undetectable HCV RNA at LT. This option was tested in the early phase of DAAs development. In a study, SOF plus RBV was used in 61 LT candidates (genotype 1: 74%) listed for compensated cirrhosis with hepatocellular carcinoma, until the time of LT or for up to 48 weeks [39]. Fifteen patients discontinued treatment before LT, in 9 cases for virologic failure; 46 patients underwent LT and were studied for HCV recurrence rates. Of these, 43 and 30 had undetectable HCV RNA at the time of LT, and 12 weeks after LT, respectively. The best predictor of SVR was the number of consecutive days with undetectable HCV RNA before LT. Patients with more than 30 days of HCV RNA undetectability had a 95% chance of no HCV recurrence after LT.

The period of time between initiation of antiviral therapy and LT is not predictable leading some patients to not complete the full course of treatment. Therefore, some authors evaluated the effectiveness and safety of continuing treatment with DAAs after LT. Fernandez-Carrillo et al. reports 15 patients, mainly infected by genotype 1, who received antiviral therapy pre-LT continued post-LT, most commonly SOF + DAC (n = 8), for 24 weeks [51]. LT was performed after a median of 4 (range, 1–16) weeks of treatment. Twelve patients were HCV RNA negative at the time of LT. Treatment was discontinued temporarily after LT for a median of 5 (range, 2–33) days. Fourteen patients (93%) achieved SVR and treatment was generally well tolerated.

11.1.2.4 Posttransplant Antiviral Treatment

After LT, two strategies are possible: preemptive antiviral therapy before the occurrence of hepatitis on the graft or mainly treatment of chronic hepatitis on the graft. Patients with fibrosing cholestatic hepatitis and patients with moderate to extensive fibrosis require rapid antiviral therapy. If a liver graft biopsy is not performed, noninvasive markers can help to make the treatment decision. A cut-off value of 8.7 kPa for liver stiffness had sensitivity and a negative predictive value for significant fibrosis and portal hypertension >0.90 in all cases [52].

Preemptive Treatment

Levitsky et al. reports 16 patients receiving a single dose of SOF + LED at the time of LT and once daily for 4 weeks postoperatively [53]. Fifteen of the 16 patients achieved SVR 12 and one had a relapse. Serious adverse events were observed in 31% of patients, however, no patient discontinued treatment related to an adverse event, had graft loss, or died. In the SOLOFT study, 20 patients received SOF + RBV on the same day as LT and for the following 24 weeks [54]. All patients showed a response at the end of treatment. A limiting factor of this option is that post-LT complication may delay the start of treatment.

Treatment of Established Infection on the Graft

Antiviral C therapy should be initiated in the presence of histologically proven HCV recurrence. The decision to initiate antiviral therapy should also take into account the patient's general condition, level of hemoglobin, renal function, immunosuppression, DDIs, previous antiviral therapy failure, HCV genotype, and the stage of fibrosis.

IFN-based regimens are no more used to treat HCV infection post-LT related to lower efficacy and poor tolerability.

Results of antiviral combination using SOF with a second DAA (LED, DCV, SIM) +/− RBV or 3D are reported in Table 11.1.

SOLAR-1 study reported the efficacy and safety of LDV, SOF, and RBV during 12 or 24 weeks for 223 transplanted patients infected by genotype 1 or 4 without cirrhosis (n = 111), with Child-Pugh A cirrhosis (n = 51), Child-Pugh B cirrhosis (n = 52), Child-Pugh C cirrhosis (n = 9), or CH (n = 6) [18]. SVR 12 was achieved by 96 and 98% of patients without cirrhosis or Child-Pugh A cirrhosis, by 85 and 88% of patients with Child-Pugh B cirrhosis, by 60 and 75% of patients with Child-Pugh C cirrhosis and by all patients with CH receiving 12 or 24 weeks of therapy, respectively. Twelve weeks of therapy was as effective as 24 weeks. Relapse occurred in 7% of patients with baseline RASs as compared with 4% in patients without baseline RASs. No relapses were observed for patients who received 24 weeks of therapy. At the time of virological failure, among patients who relapsed, 85% were observed to have NS5A variants. No resistant variant to SOF was observed. SOLAR-2 study, including 168 patients following the same design, reports the same results [19].

In the ALLY-1 study, 53 transplanted patients (cirrhosis: 30%, genotype 1: 77%) were treated with DCV, SOF, and RBV for 12 weeks. An SVR 12 was observed in 94% of patients (genotype 1: 94%, genotype 3: 91%). Among 3 patients who relapsed, all were observed to have NS5A variants [16]. In the French prospective real-life CUPILT cohort, 512 transplanted patients (cirrhosis: 21%, genotype 1: 70%) were treated with SOF-NS5A inhibitor with or without RBV for 12 (n = 203) or 24 weeks (n = 309) [17]. An SVR 12 was observed in 96% and 95% of patients with and without RBV in the 12 weeks arm and 93% and 98% of patients with and without RBV in the 24 weeks arm. Twenty patients did not achieve an SVR 12. The majority of them had NS5A or NS3 resistance mutations. The authors concluded that SOF-NS5A inhibitor without RBV for 12 weeks constituted

Table 11.1 Results of IFN-free regimens in liver transplant recipients with hepatitis C recurrence

DAA regimen, Trial name (Reference)	Type of study	Patients	Time since LT median	Genotype	Treatment-experienced	Fibrosis stage	SVR 12	Virologic failure	SAE[a]
SOF-RBV 24 weeks [11]	Prospective, multicenter, open-label	40	4.3 years (1.0–10.6)	G1a: 55% G1b: 28%	88%	F3-F4: 62%	70%	Relapse	15%
Paritaprevir/r-ombitasvir-dasabuvir-RBV 24 weeks CORAL-1 [28]	Prospective, multicenter, open-label	34	39.5 months (12.9–136.4)	G1a: 85% G1b: 15%	71%	≤ F2	97%	RAS in NS3, NS5A and NS5B (n = 1)	6%
LDV-SOF-RBV 12–24 weeks SOLAR-1 [18]	Prospective, randomised phase 2 study	111	2.9 years 2.8 years	G1a: 72% G1b: 27%	82%	F0-F3	96% (12 w) 98% (24 w)	NS5A variants were present in 85% of patients who relapse (n = 6)	20.5%
		51	8.8 years 6.6 years	G1a: 67% G1b: 33%		F4 Child-Pugh A	96% (12 w) 96% (24 w)		
		52	5.1 years 6.3 years	G1a: 73% G1b: 25%		F4 Child-Pugh B	85% (12 w) 88% (24 w)		
		9	5.2 years 5.7 years	G1a: 78% G1b: 22%		F4 Child-Pugh C	60% (12 w) 75% (24 w)		
		6	1.1 years 0.3 years	G1a: 83%		CH	100% (12 w)		

				G1b: 17%			100% (24 w)		
LDV-SOF-RBV 12–24 weeks SOLAR-2 [19]	Prospective, randomised phase 2 study	101	3.3 years 2.7 years	G1: 88% G4: 12%	81.5%	F0-F3	93% (12 w) 100% (24 w)	NS5A variants were present in a patient who relapse	18%
		67	4.4 years 6.7 years	G1: 87% G4: 13%		F4 Child-Pugh A	100% (12 w) 96% (24 w)		
		45	8.7 years 2.5 years	G1: 89% G4: 11%		F4 Child-Pugh B	95% (12 w) 100% (24 w)		
		8	6.0 years 9.5 years	G1: 87% G4: 13%		F4 Child-Pugh C	50% (12 w) 81% (24 w)		
		5	0.4 years 0.3 years	G1: 100%		CH	100% (12 w) 100% (24 w)		
DCV-SOF-RBV 12 weeks ALLY-1 [16]	Prospective, multicenter, open-label	53	4 months to > 13 years	G1a: 58% G1b: 19% G3: 21%	58%	F3-F4:55%	94% G1: 95% G3: 91%	NS5A variants were present in all patients who relapse (n = 3)	9%
SOF-NS5A (LED or DCV) +/− RBV	Prospective, multicenter, real-life cohort	512 SOF-NS5A	Mean 85+/−72.1 months	G1: 70% G3: 18% G4: 10%	34%	F3-F4:36%	SOF-NS5A 12 weeks:	20 patients	24.8%

(continued)

Table 11.1 (continued)

DAA regimen, Trial name (Reference)	Type of study	Patients	Time since LT median	Genotype	Treatment-experienced	Fibrosis stage	SVR 12	Virologic failure	SAE[a]
12–24 weeks CUPILT [17]		12 weeks: 156 24 weeks: 239 SOF-NS5A +RBV 12 weeks: 47 24 weeks: 70					95% 24 weeks: 98% SOF-NS5A +RBV 12 weeks: 96% 24 weeks: 93%		
DCV-SOF +/− RBV (n = 77) DCV-SIM +/− RBV (n = 18) DCV-SIM-SOF (n = 2) 24 weeks [20]	Retrospective, multicenter, real-life cohort	97	Mean 44.5 +/− 55 months	G1: 93%	NA	F4: 31% CH: 37%	87% F4: 91% CH: 72%	Relapse n = 2 Breakthrough n = 3 in DCV – SIM regimen	20.6%
SIM-SOF +/− RBV (RBV n = 25) 12 weeks [14]	Prospective, multicenter, real-life cohort	123	32 months (2–317)	G1a: 60% G1b: 35%	82%	F3-F4:30%	90% F0-F2: 93% vs F3-F4: 81% (p = 0.05)	Relapse n = 8 Breakthrough n = 1	2%
SIM-SOF +/− RBV (119/32) 12–24 (n = 15)	Prospective, multicenter, real-life cohort	151	Mean 5 (0–23) years	G1: 100%	56%	F4: 64%	88%	Relapse n = 11	11.9%

weeks HCV-TARGET [21]								Breakthrough n = 1	
SIM-SOF +/− RBV (n = 3) 12 weeks [13]	Retrospective, single center, real-life cohort	61	5.4 (1.9–8.4) years	G1: 100%	69%	F3-F4: 38%	93% G1b: 100% G1a ≤ F2: 100% G1a > F2: 67%	Relapse n = 4	9.8%
SIM-SOF+/− RBV 12 weeks (n = 53) SOF-RBV+/− PegIFN 24 weeks (n = 61) LED-SOF 12–24 weeks (n = 6) [22]	Retrospective, multicenter, real-life cohort	120	49.4 +/ −53.7 months	G1: 83%	82%	F3-F4: 48%	85% G1a: 83% G1b: 100%	Relapse n = 7	11%
LDV-SOF +/− RBV (n = 45) 8 weeks n = 7 12 weeks n = 108 24 weeks n = 47 [15]	Retrospective, single center, real-life cohort	162	Mean 4.8 years	G1: 96%	49%	F3-F4: 20%	96%	Relapse n = 4	8.3%
LDV-SOF +/− RBV (n = 309) DCV-SOF +/− RBV (n = 32) 3D +/− RBV (n = 16)	Prospective, multicenter, real-life cohort	357	NA	G1: 87%	58%	F4: 44%	96%	NA	10%

(continued)

Table 11.1 (continued)

DAA regimen, Trial name (Reference)	Type of study	Patients	Time since LT median	Genotype	Treatment-experienced	Fibrosis stage	SVR 12	Virologic failure	SAE[a]
HCV-TARGET [23]									
SOF-VEL 12 weeks [55]	Prospective, phase 2 open-label study	79	7.5 (0.3–23.9) years	G1: 47% G3: 44%	59%	F4: 18%	G1: 95% G3: 97%	Relapse n = 2	4%
GLE-PIB 12 weeks Magellan-2 [56]	Prospective, phase 3 open-label study	80	53.8 (4.2–213.7) months	G1: 51% G3: 28%	38%	F0-F1:78% F2: 8% F3: 15%	97.5%	Relapse n = 1	8%

DAA: direct-acting antiviral, LT: liver transplantation, SVR: sustained virologic response, SOF: sofosbuvir, RBV: ribavirin, PEG-IFN: pegylated interferon, PI: protease inhibitor, NS5A: NS5A inhibitors, NA: not available, SIM: simeprevir, DCV: daclatasvir, LDV: ledipasvir, VEL: velpatasvir, GLE: glecaprevir, PIB: pibrentasvir, CH: cholestatic hepatitis

[a]Serious adverse events (SAE) were considered unrelated to study treatment but related to liver decompensation

reliable therapy for recurrent HCV post-LT whatever the fibrosis stage, HCV genotype, and previous HCV treatment.

Other real-world studies have supported high rates of SVR and excellent tolerability of DAA regimens in LT recipients including combination regimens of SOF-LDV [15, 23], SOF-SIM [13, 14, 21, 22, 24, 25], SOF-DCV [20, 27], SOF-SIM-DCV [26], and 3D [28].

The HCV drug combinations actually recommended are SOF-VEL and GLE-PIB. In a study, 79 liver transplant recipients with recurrent genotypes 1–4 HCV infection were treated with the fixed-dose combination of SOF and VEL for 12 weeks without RBV [55]. The SVR rate was 96% (76/79; 2 relapses). Age, gender, HCV genotype, cirrhosis status, pretreatment RASs, and prior treatment experience had no clinically relevant effect on SVR. No clinically significant DDIs were observed between this combination and immunosuppressive agents. RBV should be added to SOF-VEL in case of decompensated cirrhosis [29, 30]. Patients with contraindications for RBV or poor tolerance to RBV could be treated with SOF-VEL for 24 weeks. The Magellan-2 study reports 80 LT recipients with recurrent genotype 1–6 HCV infection, without graft cirrhosis on a stable immunosuppressive regimen treated with GLE-PIB [56]. Seventy nine achieved SVR (98%). The efficacy of GLE-PIB regimen was unaffected by HCV genotype, baseline polymorphisms in NS3 and/or NS5A or previous treatment experience. GLE-PIB regimen demonstrates high efficacy, a favorable safety profile, and minimal interaction with concomitant immunosuppressive drugs.

The natural history of CH recurrence was also transformed by the availability of DAAs. Severe CH is now treatable and SVR is attainable in the vast majority of patients [11, 18, 19, 57]. In the study of Leroy et al., 23 patients (genotype 1: 78%, 4 patients coinfected with HIV, median time since LT: 5.3 months) with CH were given either SOF and DCV (n = 15) or SOF and RBV (n = 8) for 24 weeks [57]. All patients survived, without re-transplantation until week 36. Dramatic improvement in clinical status was observed and 22 patients (96%) achieved an SVR. One relapse occurred in a patient treated with SOF and RBV.

Based on the results of these studies, HCV management guidelines for posttransplant patients were reported by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) [29, 30] (Table 11.2).

In conclusion, DAAs combination regimens appear to be highly effective in LT recipients (SVR > 90–95%) even in patients with CH or decompensated cirrhosis [11, 18, 19]. Safety profiles are similar and favorable among all DAAS regimens. However, some limitations should be highlighted.

11.1.2.5 Unmet Medical Needs Regarding DAA in Transplant Recipients

Treatment Duration and the Use of Ribavirin

Twelve weeks seems to be the optimum duration of antiviral therapy. No risk factor of treatment failure has been identified for actual DAAs regimens. It is anticipated

Table 11.2 Recommended regimens for treatment of HCV infection in liver transplant recipients according to AASLD and EASL guidelines

	Regimen	Guidelines
Genotype 1–6 infection in the graft without cirrhosis	GLE-PIB 300–120 mg daily, 12 weeks	AASLD, EASL
	SOF-VEL 400–100 mg daily, 12 weeks	AASLD, EASL
	SOF-LED 90–400 mg daily, 12 weeks (genotype 1,4,5,6)	AASLD
Genotype 1–6 infection in the graft with compensated cirrhosis	GLE-PIB 300–120 mg daily, 12 weeks	AASLD, EASL
	SOF-VEL 400–100 mg daily, 12 weeks	AASLD, EASL
	SOF-LED 90–400 mg daily, 12 weeks (genotype 1,4,5,6)	AASLD
Genotype 1–6 infection in the graft with decompensated cirrhosis	SOF-LED-RBV 90-400-600 mg daily, 12 to 24 weeks (genotype 1,4,5,6)	AASLD
	SOF-VEL-RBV 400-800-600 mg daily, 12 to 24 weeks	AASLD, EASL (12 weeks or 24 weeks without RBV)

Refs: [29, 30]

that early post-LT HCV therapy will lead to most patients being treated before they develop advanced fibrosis/cirrhosis and will thus optimize the results of therapy.

DAAs regimens without RBV are recommended. However, RBV should be used in association with SOF-VEL for patients with decompensated cirrhosis.

Drug–Drug Interactions

Drug–drug interaction remains an issue post-LT, besides they are less potent using new generation DAAs compared to first-generation PIs. Recipients of liver graft should take life-long immunosuppressive drugs and many other drugs to treat various comorbidities. All these drugs must be checked to possible DDI with DAAs [58]. Except SOF, second-generation PIs and NS5A inhibitors are substrates and inhibitors of CYP-3A4 and Pg-p metabolic pathways and thus could interact with several drugs, such as immunosuppressive drugs [58]. Variations of AUC of CNI are mainly observed using PIs (Table 11.3).

Usually, DAA has a liver metabolism. The use of PIs in Child C patients is currently not recommended. SOF has no hepatic metabolism but a renal one. SOF is not recommended in patients with creatinine clearance below 30 ml/min until an appropriate dosage is determined.

Finally, nonadherence leads to suboptimal exposure to antiviral drugs. It is associated with treatment failures and the emergence of RASs, especially during the early phase of treatment. Treatment adherence must be enhanced [59].

Table 11.3 Potential drug-drug interactions between calcineurin inhibitors and direct-acting antiviral drugs

	Cyclosporine	Tacrolimus
Sofosbuvir	No clinically relevant interaction	No clinically relevant interaction
Sofosbuvir/ ledipasvir	No clinically relevant interaction	No clinically relevant interaction
Velpatasvir	No clinically relevant interaction	No clinically relevant interaction
Glecaprevir/ pibrentasvir	5-fold increase in Glecaprevir AUC with high doses of Cyclosporine (>100 mg/d) Not recommended	1.45-fold increase in Tacrolimus AUC Monitor Tacrolimus levels
Sofosbuvir/ velpatasvir/ voxaliprevir	9.4-fold increase in Voxaliprevir AUC Not recommended	Not known Monitor Tacrolimus levels

Ref: http://www.hep-druginteractions.org/

Virologic Failure

Using new DAAs combination regimens, virological failure is now a very rare event. However, transplant recipients have high viral loads, making it easier to select for RASs. Some cases of virologic failure have been reported related mainly to PIs or NS5A RASs [11, 16–19, 28]. The choice of the IFN-free regimen should be determined by previous antiviral treatment failure(s). Related to a high barrier to resistance, resistant HCV variants have been exceptionally reported with SOF, and they rapidly disappeared after treatment cessation. Thus, retreatment strategies should include SOF. In contrast, patients treated with a PI or an NS5A inhibitor who failed to achieve SVR select viruses with RASs in the NS3 protease or NS5A, respectively, which confer drug resistance. Viruses resistant to PI decrease in proportion to become undetectable within a few months to 2 years after treatment cessation. In contrast, viruses resistant to NS5A inhibitors are fit and remain dominant for many years, after they have been selected. Patients who failed on a previous DAA-containing regimen should be retreated with a drug with a high barrier to resistance (currently, SOF), plus one or two other drugs, such as VEL-VOX or GLE-PIB. SOF-VEL-VOX is currently recommended for treatment of HCV in difficult-to-treat patients such as patients with compensated cirrhosis infected with genotype 3 carrying the Y93H RAS combined with other NS5A RASs or patients with rare subtypes (i.e., 1l, 4r, 3b, 3g, 6u. . .) naturally harboring one or several NS5A RASs. However, the use of this regimen in the post-LT setting is limited [60].

11.1.3 Management of Human Immunodeficiency Virus/HCV Coinfected Liver Transplant Recipients

Since the introduction of combined antiretroviral therapy (ART) in the mid-1990s and the drastic reduction in mortality by human immunodeficiency virus (HIV) infection, liver disease, particularly those related to HCV infection, have become a leading cause of death in HIV-infected individuals [61]. LT has been increasingly performed in coinfected patients with decompensated cirrhosis or hepatocellular carcinoma. Coinfected patients should be referred for LT early after the first episode of hepatic decompensation. HIV-specific criteria for LT include HIV RNA suppressible by ART, a CD4+ T-cell count >1–200/μl, and no history of AIDS defining events. Historically, survival in HIV/HCV coinfected patients was poorer than in HCV mono-infected patients due to a more aggressive HCV recurrence that leads to graft loss and death [34, 62–64]. The high efficacy of antiviral C therapy using new DAAs was a major breakthrough in the natural history of HIV–HCV coinfection. SOF-VEL or GLE-PIB are highly effective in treatment-naïve or treatment-experienced patients with cirrhosis coinfected with HCV and HIV leading to SVR rates over 95%. Thus, the majority of coinfected patients awaiting LT are HCV RNA negative. Few studies are reported using DAAs in the waiting list and post-LT HIV/HCV coinfected patients [65–67]. However, studies in non-transplant patients suggest that HIV infection does not negatively affect SVR rates. SOF and NS5A inhibitors do not interact with ART regimens and are the current regimens of choice [58]. In contrast, PIs could interact with ART regimens and should be used cautiously. Advice from an HIV expert is highly recommended to avoid DDIs between ART regimen and immunosuppressive drugs or anti-HCV antiviral treatment.

11.1.4 HCV Antibody-Positive Donors

In an effort to expand the liver donors pool and to reduce waiting times and mortality in the waiting list, expanded criteria donors such as donors infected with hepatitis B virus or HCV are increasingly used [68]. However, the use of HCV positive liver grafts has been limited by health authorities to HCV infected recipients and after an informed consent. The prevalence of HCV is higher among organ donors than the general population (5.58% vs. 3.45%) [69]. Several studies have shown that both patient and graft survival of HCV-positive recipients are not affected by the HCV serostatus of the donor [68]. These results may be related to the presence of a significant proportion of HCV RNA-negative donors, the use of strict criteria such as younger donor age, normal liver tests, donor liver biopsy at the time of procurement. Since HCV RNA does not integrate the host genome and that there is no HCV residual viral particle after SVR, the risk of HCV transmission using HCV RNA-negative donors is extremely low. Using DAAs, the number of HCV RNA-negative, anti-HCV positive donors should increase. Yet, HCV positive livers have remained under-used related to the risk of an aggressive course of HCV infection after transplantation, the risk of treatment failure after LT (particularly

for genotype 3) and HCV treatment costs. The high efficacy of DAA regimens may render HCV positive liver grafts safer and may extend the use of such grafts even in HCV-negative recipients.

11.2 Conclusion

Historically, posttransplant HCV recurrence was a constant and severe complication and was the primary cause of graft loss and death in these patients. Pegylated interferon-RBV and first-generation NS3/4 PI: BOC or TVR associated with PEG-IFN-RBV are no more used to treat HCV infection after LT related to lower efficacy, poor tolerability, and DDIs with immunosuppressive drugs. In contrast, news DAAs regimens using SOF-VEL or GLE-PIB, have very high efficacy, lower toxicity, and DDIs in pre- and posttransplant settings and have changed dramatically the face of LT for hepatitis C. The goal of antiviral therapy with new DAAs regimens should be: first, viral eradication before LT to prevent graft reinfection and possibly in some patients, rescue to LT; second, viral eradication post-LT to improve long-term graft and patient survival and reduce the need for re-LT. Some infrequent cases of viral mutations have been reported using DAAs combination regimens pre- or post-LT that can lead to difficulties in the management of these patients.

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Management of Patients with Renal Impairment: Direct-Acting Antivirals and Renal Function

12

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Abbreviations

CHC	Chronic HCV infection
DAAs	Direct-acting antiviral agents
GFR	Glomerular filtration rate
HCV	Hepatitis C virus
KT	Kidney transplantation
PEG-IFN	Pegylated interferon-α
RBV	Ribavirin
SVR	Sustained virological response

Chronic hepatitis C virus (HCV) infection is associated with several extrahepatic manifestations, such as diabetes mellitus, lymphoproliferative disorders, and cardiovascular adverse events supporting the concept that HCV infection is a systemic disease with relevant extrahepatic consequence [1]. In addition, patients with chronic HCV infection have an increased risk of proteinuria and chronic kidney disease (CKD), while it seems that the rate of CKD progression to end-stage renal disease (ESRD) and hemodialysis (HD) is higher in chronic HCV patients, compared to noninfected patients [1]. Thus, the Kidney Disease Improving Global Outcomes

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(KDIGO) guidelines suggest screening for creatinine clearance and proteinuria among patients with chronic hepatitis C (CHC) [2]. On the other hand, the prevalence of HCV infection is higher in patients with ESRD and HD patients compared to the general population [3], while CHC has been related with higher morbidity and worse survival in both ESRD patients and kidney transplant (KT) recipients, compared to noninfected patients [1].

HCV treatment in patients with renal dysfunction was a challenging issue in the era before the direct-acting antiviral (DAAs), since interferon-alpha (IFN) or pegylated IFN (PEG-IFN) with or without ribavirin (RBV) even in low doses (200–400 mg three times weekly) was associated with low rates of sustained virological response (SVR) (up to 60%) and several serious and potentially life-threatening adverse events [3]. Moreover, IFN therapy has been contraindicated in KT recipients due to the risk of acute rejection of kidney graft [4, 5].

After 2014, newer DAAs have been licensed for the treatment of CHC by both EMA and FDA (Table 12.1). These antiviral agents are given with or without RBV for 8–24 weeks offering very high (>95%) SVR rates in most subgroups of CHC patients. All DAAs are mainly eliminated through the liver, except for sofosbuvir which is eliminated through the kidneys [6]. Nevertheless, all available DAAs do not require dose adjustment in patients with GFR >30 mL/min and treatment recommendations are identical between patients with mild or moderate renal impairment and those with normal renal function [6]. However, in patients with severe renal impairment [estimated GFR (eGFR) <30 mL/min/1.73 m2] and/or patients requiring hemodialysis, sofosbuvir and consequently its co-formulations, ledipasvir/sofosbuvir, velpatasvir/sofosbuvir and velpatasvir/voxilaprevir/sofosbuvir should not be used, while simeprevir should be given with caution, since literature data regarding its effect on renal function in this group of patients is limited [6].

12.1 Impact of DAAs on Renal Function

12.1.1 Non-Transplant Setting

Sofosbuvir-based regimens have been mainly evaluated for potential effects on renal function, since sofosbuvir is the only DAA regimen with renal elimination. In one study [7], renal dysfunction (defined as increase in serum creatinine ≥50% from DAAs initiation) was observed in 4% of the 152 patients (most of them with baseline eGFR ≥60 mL/min) who received sofosbuvir-based regimens. In multivariable analysis, only ascites [odds ratio (OR): 3.16] and preexisting proteinuria (OR: 5.74) were significantly associated with development of renal dysfunction. Finally, in another study [8], 52 patients with HCV decompensated cirrhosis were treated with sofosbuvir and an NS5A inhibitor (ledipasvir or daclatasvir) plus RBV for 12 weeks. Cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) levels increased from baseline to week 4 of therapy (cystatin C: 1.46 vs. 1.55 mg/L, $p < 0.01$; NGAL: 28.1 vs. 32.8 ng/mL, $p < 0.01$) indicating transient renal

Table 12.1 Main characteristics of the approved direct-acting antivirals (DAAs) currently used for the treatment of hepatitis C

DAA (commercial name), dose	Dose adjustment in renal impairment	CNIs coadministration
Sofosbuvir (Sovaldi®), tablet 400 mg, once daily	Contraindicated if GFR <30 mL/min	No change
Simeprevir (Olysio®), tablet 150 mg, once daily with food	No change in renal impairment	Contraindicated with cyclosporine
Daclatasvir (Daklinza®), tablet 60 mg, once daily	No change in renal impairment	No change
Ledipasvir/Sofosbuvir/ (Harvoni®), tablet 90/400 mg, once daily	Contraindicated if GFR <30 mL/min	No change
Ombitasvir/Paritaprevir/ritonavir (Viekirax®), tablet 12.5/75/50 mg, two once daily with food	No change in renal dysfunction	Cyclosporine: 20% of pretreatment total daily dose; tacrolimus: 0.2 mg/72 h or 0.5 mg once weekly
Dasabuvir (Exviera®), tablet 250 mg, every 12 hours	No change in renal dysfunction	
Elbasvir/Grazoprevir (Zepatier®), tablet 100/50 mg, once daily	No change in renal dysfunction	Coadministration increases tacrolimus concentrations
Velpatasvir/Sofosbuvir/ (Epclusa®), tablet 100/400 mg, once daily	Contraindicated if GFR <30 mL/min	No change
Glecaprevir/Pibrentasvir (Mavyret®), tablet 100/40 mg, once daily	No change in renal dysfunction	It is not recommended in cyclosporine doses >100 mg per day
Sofosbuvir/Velpatasvir/ Voxilaprevir (Vosevi®), tablet of 400/100/100 mg, once daily	Contraindicated if GFR <30 mL/min	Contraindicated with cyclosporine

CNI: Calcineurin inhibitor

dysfunction. According to these findings, it might be suggested that monitoring of renal function and standard nephroprotective measures may be useful when sofosbuvir-based regimens are applied, particularly in patients with ascites or preexisting kidney disease.

On the other hand, eradication of HCV infection after antiviral therapy may have a beneficial impact on GFR, irrespectively of DAA regimen (sofosbuvir based or not). Such an effect has been suggested by a study presented only as an abstract and including data from 9 clinical trials with the ombitasvir/paritaprevir/dasabuvir-based regimens in patients with or without GFR less than 60 mL/min but not under HD. In multivariable analysis, baseline proteinuria, body mass index, and black race were independently associated with an improvement of GFR more than 10 mL/min. Thus, according to these data, some DAA regimens might directly or probably indirectly lead to some improvement of renal function in patients with moderate renal insufficiency [9]. Similarly, in another recent study [10] including 124 patients treated with

DAAs, SVR was associated with GFR improvement (78.55 ± 8.96 at baseline vs 81.85 ± 12.87 mL/min at SVR week 12, p = 0.037).

12.1.2 Transplant Setting

The effect of sofosbuvir-based antiviral regimens on renal function was assessed in liver transplant (LT) recipients who are at high risk for renal impairment due to the chronic use of calcineurin inhibitors. In a recent study [11] including 193 LT recipients with HCV recurrence treated with sofosbuvir-based regimens, baseline GFR (OR = 1.02) was independently associated with development of renal dysfunction. In another study with 165 LT patients with HCV recurrence [12] under sofosbuvir-based regimens, worsening renal function was observed more frequently in those with baseline GFR <30 mL/min (p = 0.01) and cirrhosis (p = 0.01). Renal function improvement after treatment was observed more commonly in those who achieved SVR, compared to those who did not (81% vs 19%, p < 0.05).

12.2 Interferon-Free Regimens in Patients with CHC and CKD (Table 12.2)

12.2.1 Interferon-Free Regimens Approved for CHC and CKD

12.2.1.1 Ombitasvir/Paritaprevir/Dasabuvir-Based Regimens

The combination of ombitasvir/paritaprevir/ritonavir, which has been abbreviated as 2D regimen, is used (with RBV) for the treatment of genotype 4 CHC patients, while in combination with dasabuvir (abbreviated all together as 3D) is given for the treatment of genotype 1a or 1b CHC patients (with or without RBV, respectively). Literature data have shown that no dose adjustment for the 3D or 2D regimens is required in the presence of severe renal impairment. In the RUBY-I study [13], 3D was given in 20 genotype 1 treatment-naïve non-cirrhotic patients with CHC and CKD stage 4 or 5 (RBV was given at 200 mg/day in genotype 1a patients; 13 patients were on HD) for 12 weeks. SVR rate was high (90%) and none of the nine serious adverse events observed in four patients was related to antiviral therapy. No deterioration of liver or kidney function was recorded during the study period. More recently, the cohort 2 RUBY-I and RUBY-II trials [14, 15] were presented as abstracts. In cohort 2 RUBY-I [14], 48 patients with CKD stage 4 or 5 (including cirrhotics and treatment-experienced patients) were evaluated. SVR rate was excellent (96%) with good safety profile. In the RUBY-II cohort [15], 3D or 2D regimens (without RBV) were evaluated in CKD stage 4 or 5 patients with HCV genotype 1a or 4, respectively. All patients (n = 18) were naïve and non-cirrhotics. SVR12 rate was 94% and no serious adverse events were observed related to antiviral regimens, indicating that RBV maybe not needed in genotypes 1a and 4 patients with severe renal impairment.

Table 12.2 Studies of interferon (IFN)-free regimens for treatment of HCV patients with severe renal disease or under hemodialysis

Study	Patients, n	Patient characteristics	Regimen: patients number (Dose of sofosbuvir)	Sustained virological response at 12 weeks, n/N	Adverse events, n
Pockros et al. [13]	20	GT1: 20 patients (1a: 13)	3D ± RBV: 20	18/20 (EOT-VR: 20/20)	Death from drug unrelated cause (cardiac arrest at 14 days after the end of therapy): 1
Gomez et al. [16]	33	GT1: 29 (1a: 6) Age: 57 years	3D ± RBV: 33	31/31	Serious adverse events: 5 (all unrelated to study drugs)
Basu et al. [17]	36	GT1: 36 (1a: 23)	3D ± RBV: 36	34/36	No serious adverse event
Roth et al. [18]	122	GT1: 122 patients	Elbasvir/Grazoprevir: 122	115/122	Serious adverse events: 16
Czul et al. [23]	28	GT1: 26 (1a: 16) Age: 58 years	SOF + SMV: 26 SOF + RBV: 2 (200 mg/eod-400 mg/day)	21/25	Encephalopathy: 1, Uncontrolled diarrhea: 1
Beinhardt et al. [24]	15	GT1: 11 patients Age: 52 years	SOF + DCV: 9 SOF + SMV: 5 SMV + DCV: 1 (400 mg/day)	1/1 (EOT-VR: 5/5)	Pancytopenia at week 7: 1 (change SOF from every 24 h to every 48 h)
Dumortier et al. [25]	50	GT1: 28 patients Age: 60 years	SOF + RBV: 7 SOF + RBV + PEG-IFN: 2 SOF + DCV ± RBV: 30 SOF + SMV ± RBV: 11	24/26 (EOT-VR: 50/50)	No serious adverse event
Gane et al. [26]	10	GT1: 9 (1a: 7) Age: 62 years	SOF + RBV: 10 (200 mg/day)	4/10	Serious adverse events: 2 (diabetic acidosis, angina)
Nazario et al. [27]	40	GT1: 26 (1a: 26) Age: 57 years	SOF + LDV: 9 SOF + DCV: 2 SOF + SMV: 29 (400 mg/day)	29/29	Drug discontinuation: 1 (unknown reason)
Baliellas et al. [28]	21 (10 on hemodialysis)	GT1: 20 patients (1a: 2) Age: 57 years	SMV + DCV:12 SMV + DCV + RBV: 9	17/19	No serious adverse event

(continued)

Table 12.2 (continued)

Study	Patients, n	Patient characteristics	Regimen: patients number (Dose of sofosbuvir)	Sustained virological response at 12 weeks, n/N	Adverse events, n
Moreno et al. [29]	42	GT1: 25 (1a: 8) Age: 54 years	SOF + RBV: 5 LDV/SOF: 8 SOF + DCV: 14 SOF + SMV: 3 SMV + DCV: 12	32/42	Drug discontinuation: 11
Saxena et al. [22]	19	GT1: 16 (1a: 8)	SOF + SMV + RBV: 2 SOF + SMV: 11 SOF + RBV: 5 SOF + RBV + PEG-IFN: 1 (400 mg/day)	SOF + SMV + RBV: 2/2 SOF + SMV: 8/10 SOF + RBV: 4/4 SOF + RBV + PEG: 1/1	Therapy discontinuation: 1, Serious adverse events: 3
Martin et al. [30]	10	GT1: 8 patients Age: 58 years	SOF + RBV: 10 (400 mg/day)	6/10	Acute respiratory failure—drug discontinuation: 1, Hematemesis: 1

DCV: daclatasvir, EOT-VR: end of treatment virological response, GT: genotype, RBV: ribavirin, LDV: ledipasvir, PEG-IFN: pegylated interferon-alfa, SMV: simeprevir, SOF: Sofosbuvir, 3D: ombitasvir/paritaprevir/ritonavir plus dasabuvir, eod: every other day

Finally, real-life data have been reported from two studies [16, 17] including in total 69 CHC genotype 1 patients with stage 4 or 5 CKD (i.e., GFR <30 mL/min) under 3D (with or without RBV) regimen [29 (44.6%) with genotype 1a]. 3D with or without RBV was given for 12 weeks in 32 (46.3%) patients [16, 17]: SVR rates were 97% (65/67) [(94.4% (17/18) for 3D and 94.4% (17/18) for 3D plus RBV, while the safety profile was excellent, since no patient discontinued 3D regimen.

12.2.1.2 Elbasvir/Grazoprevir

Elbasvir/grazoprevir (co-formulated in one tablet) are cleared by the liver, and thus they are considered as a good option for patients with CKD stages 4 and 5. This was demonstrated in the C-SURFER phase III study[18], in which 224 patients with GFR <30 mL/min were randomized to receive elbasvir/grazoprevir (n = 111) or placebo (n = 113) for 12 weeks. At week 16, all patients in the placebo arm were converted to the active drug as well. Fifty-two percent of the patients had genotype 1a, 83% were treatment-naïve, 6% had cirrhosis and 81% had CKD stage 5 (76% of them under HD). SVR was achieved in 94% (115/122) of patients in the active arm, while serious adverse events were observed in 16 (14%) and 17 (15%) patients in the elbasvir/grazoprevir and placebo arms, respectively ($p > 0.05$). None of the patients in the active arm discontinued therapy due to an adverse event. The most common adverse events in the active arm were headache, nausea, and fatigue. There were also four reported deaths, but none were considered related to study drug.

12.2.1.3 Glecaprevir/Pibrentasvir

This fixed combination has pangenotypic antiviral activity and a high barrier to resistance. It is given without RBV and no dose adjustment is needed in CHC patients with ESRD. This was clearly shown in a recent multicenter, open-label, phase 3 trial, in which glecaprevir and pibrentasvir were given for 12 weeks in 104 CHC patients with genotypes 1–6 (52% genotype 1, 16% genotype 2, 11% genotype 3) with compensated liver disease (with or without cirrhosis) and severe renal impairment (stage 4 or 5 with or without under HD). SVR was excellent (98%) without any virologic failure during treatment or relapse after the end of treatment. Serious adverse events were reported in 24% of the patients and adverse events reported more than 10% were pruritus, fatigue, and nausea. Of the four patients who discontinued this regimen prematurely due to adverse events, three achieved SVR [19].

12.2.2 Interferon-Free Antiviral Regimens Not Approved for CHC and CKD

Sofosbuvir-based regimens have been used in CHC patients with CKD, despite the official contraindication of sofosbuvir in patients with GFR <30 mL/min or under HD [20], due to an up to 20-fold accumulation of the sofosbuvir metabolite GS-331007 in such cases. However, the clinical impact of GS-331007 accumulation is not well understood, while in our recently published review, we showed that the

efficacy of sofosbuvir-based regimens in patients with GFR <30 mL/min or under HD was comparable with those with normal renal function, while only a small proportion of patients discontinued therapy or developed serious adverse events without drug discontinuation [20]. In fact, sofosbuvir at the standard dose of 400 mg/day might be suggested in this group of patients given that lower dosage could reduce the liver concentrations of the active sofosbuvir metabolite, GS-461203 [21], while no major issue was raised using a different dosage of sofosbuvir in patients with severe renal impairment. However, most of the studies included a small number of patients, and in the largest "real world" HCV-TARGET study [22] including 73 patients with GFR of 45 mL/min treated with sofosbuvir-based regimen worsening of renal function and serious adverse events were at least 3.5 times more common among patients with GFR ≤ 45 mL/min, compared to those with GFR >45 mL/min, raising concerns for toxicities from the accumulation of sofosbuvir and its metabolites. It should be mentioned that studies reporting the use of sofosbuvir in patients with CKD stage 4/5 included few patients with genotype 2 or 3.

Several studies have evaluated the safety and efficacy of various sofosbuvir-based antiviral schemes in patients with stage 4 or 5 CKD (i.e., GFR <30 mL/min) or under HD [22–30], as such regimens were the only treatment option in the first year of DAAs era and there was no other treatment option for such patients with genotype 2, 3, 5, or 6 until the recent approval of glecaprevir/pibrentasvir. Sofosbuvir was given for 12–24 weeks [from 200 mg every other day to full dose (400 mg/day) with or without RBV] in combination with other DAAs (i.e., simeprevir, daclatasvir, or ledipasvir). The standard daily dosage of simeprevir 150 mg and of daclatasvir 60 mg was given to all patients, while the dose of ledipasvir was dependent on the dose of sofosbuvir. Most of the patients had genotype 1 CHC and almost half of them were cirrhotics and treatment naïve. Regarding efficacy, SVR at week 12 was 87.1% [92.1% with simeprevir, 100% with ledipasvir, and 85.7% with daclatasvir]. Regarding safety, a minority of patients (6%) discontinued sofosbuvir-based therapy, while 3.4% developed serious adverse events requiring hospitalization but without treatment discontinuation.

The safety and pharmacokinetics (PK) of velpatasvir has been evaluated in 10 healthy subjects with GFR <30 mL/min [31] showing that velpatasvir was well tolerated, with only 50% increase in the velpatasvir area under the curve and with only mild adverse events. Based on these findings the authors concluded that velpatasvir could be administered without dose adjustment in patients with renal dysfunction. However, since velpatasvir is available only in co-formulation with sofosbuvir, its use is driven by the limitations of sofosbuvir in patients with severe renal impairment.

12.3 Interferon-Free Regimens in Kidney Transplant Recipients with CHC (Table 12.3)

Only very few studies have evaluated the safety and efficacy of newer DAAs in Kidney Transplant (KT) recipients [32–42]. In 11 studies, a total number of 390 KT recipients with CHC received DAAs-based regimens for 12–24 weeks. Most of them had genotype 1 (301 out of 341 patients [88.2%; 83/203 (40.8%) genotype 1a] [32–39, 42], 56.3% (168/298) were treatment naïve [33, 35–37, 39, 40, 42]] and most of them were non-cirrhotics [81 out of 312 patients (25.9%) had cirrhosis [32, 33, 36, 37, 39, 40, 42]. Based on the available data, sofosbuvir was given with simeprevir (±RBV) in 31, daclatasvir (±RBV) in 20, and ledipasvir (±RBV) in 230 patients for 12–24 weeks, while fewer patients received the 3D (or 2D) combination (±RBV) (n = 12) [39, 41] or the combination of simeprevir and daclatasvir (±RBV) (n = 7) [39].

SVR rates were 94.2% (193/205) for sofosbuvir-based regimens ranging from 66.7% (10/15) for sofosbuvir plus RBV to 98% (158/161) for sofosbuvir/ledipasvir (with or without RBV). Interestingly, according to the HCV-TARGET study, the addition of RBV did not seem to affect SVR rates [42]. No efficacy data have been available for the 3D or simeprevir plus daclatasvir regimens [39, 41]. Very few patients [11 (2.8%) of 390 KT recipients] discontinued therapy and only 6 patients developed rejection of kidney graft. Renal and liver function tests remained stable during antiviral treatment.

12.4 Cryoglobulinemia-Related Kidney Disease

In the pre-DAAs era, mixed cryoglobulinemia syndrome (MCS) secondary to CHC was treated with PEG-IFN plus RBV, but lower SVR rates were reported, compared to patients without MCS [43, 44]. Notably, low GFR in patients with CHC-related MCS was associated with poorer tolerance, while peripheral neuropathy and skin ulcers may worsen under IFN-based regimens. There are limited literature data regarding the use of IFN-free DAA regimens (with or without RBV) in CHC patients with MCS, but with promising results on efficacy and tolerance profile so far. A study from Gragnani et al. [45] evaluated 44 CHC patients with MCS treated with sofosbuvir-based antiviral regimens. They reported a 100% SVR rate and 100% clinical response regarding vasculitis, while mild adverse events were recorded without any discontinuation of DAA regimen. In the four patients with renal involvement, improvement of the GFR was observed with proteinuria elimination. In a recent prospective multicenter study from France [46], the combination of sofosbuvir plus daclatasvir regimen given for 12–24 weeks was evaluated in 42 patients with CHC-related MCS. All patients achieved SVR without serious adverse events, while 37 patients (90%) had a complete clinical response (defined by improvement of all the affected organs involved at baseline and with no clinical relapse). Among the 5 patients with kidney involvement, 4 had a renal biopsy showing membranoproliferative glomerulonephritis and their proteinuria decreased

Table 12.3 Studies of IFN-free regimens for treatment of HCV positive kidney transplant recipients

Study	Patients, n	Patient characteristics	Regimen: patients number	Sustained virological response at 12 weeks, n/N	Adverse events, n
Huard et al. [32]	17	GT1: 16 patients (1a: 5), Age: 65 years	SOF + RBV:17 (400 mg/day)	1/6	Therapy discontinuation: 4 (3 due to pruritus, myalgia, anemia, 1 unclarified) Anemia: 8
Lin et al. [33]	15	GT1: 14 (1a: 10) Age: 55.8 years	SOF + SMV ± RBV: 12 (SOF + SMV: 9) SOF + RBV: 2 SOF + LDV: 1	13/15	No serious adverse events under therapy (1 died by massive hemorrhage 4 weeks after therapy) Proteinuria: 2 Bradycardia under amiodarone (pacemaker placement): 1
Bhamidimarri et al. [34]	14	GT1: 14 (1a:12) Age: 54 years	SOF + LDV: 13 (in 9 plus RBV) SOF + SMV: 1	13/14	No serious adverse events Therapy discontinuation: 1 Anemia: 7
Hussein et al. [35]	3	GT4: 3	SOF + RBV (400 mg/day)	3/3	No serious adverse events
Sawinski et al. [36]	20	GT1: 17 (1a: 7) Age: 57 years	SOF + SMV: 9 SOF/LDV: 7 SOF + RBV: 3 SOF + DCV: 1 (400 mg/day)	20/20	No serious adverse events
Moreno et al. [37]	12	GT1: 11 (1a: 4) Age: 53 years	SOF + SMV: 1 SOF/LDV: 8 SOF + DCV: 3 (400 mg/day)	11/12	Therapy discontinuation: 1
El-Halawany et al. [38]	11	GT1: 10 (1a:10) Age: 57.6 years	SOF + SMV: 2 SOF/LDV: 8 SOF + RBV: 1	10/11	No serious adverse events

Londono et al. [39]	74	GT1: 61 (1a: 6) Age: 54 years	SOF/LDV ± RBV: 37 SOF + DCV ± RBV: 15 SOF + SMV ± RBV: 6 SMV + DCV ± RBV: 7 SOF + RBV: 4 3 "D" or 2 "D": 5	45/46	Rejection episodes: 3
Colombo et al. [40]	114	GT1: 104	SOF/LDV	112/114	Therapy discontinuation: 1 Serious adverse events: 12
Reddy et al. [41]	50		SOF/LDV ± RBV: 42 SOF + DCV ± RBV: 1 3 "D": 7	10/10	Rejection episode: 1
Saxena et al. [42]	60	GT1: 54 (1a: 29)	Various antiviral schemes	94.5% (52/55)	Therapy discontinuation: 4 Rejection episode: 2

DCV: daclatasvir, GT: genotype, RBV: ribavirin, LDV: ledipasvir, PEG-IFN: pegylated interferon-alfa, SMV: simeprevir, SOF: Sofosbuvir, 3D: ombitasvir/paritaprevir/ritonavir plus dasabuvir, 2 "D": ombitasvir/paritaprevir/ritonavir

from 0.9 ± 0.4 to 0.2 ± 0.1 g/24 h. Hematuria disappeared in 4 of 5 (80%) patients at week 24. Kidney involvement improved in all 5 patients, of whom 80% had a complete renal response. Similar results have been observed in other clinical trials suggesting that a high proportion of patients with HCV and MCS can achieve viral eradication using DAA regimens.

However, some studies have shown that circulating cryoglobulins can persist despite SVR achievement, while complete clinical response may be observed in a low proportion of patients. For example, in a recent retrospective monocenter study from Canada [47], 18 symptomatic (10 with severe/life-threatening vasculitis), and 65 asymptomatic with HCV-related cryoglobulinemia were treated with DAA ± PEG-IFN. SVR was achieved in 89% symptomatic and 91% asymptomatic patients with excellent safety and tolerance profile. Interestingly, among symptomatic patients with SVR, clinical response was complete in only 39% and partial response in 22%. All four patients with life-threatening vasculitis required plasmapheresis and three received rituximab. The authors concluded that despite high SVR rates under DAAs-based therapy in patients with cryoglobulinemia, most patients did not achieve complete clinical or immunological response reflecting the persistence of cryoglobulins and/or a delay to clinical response particularly in those with severe/life-threatening vasculitis. Nevertheless, DAAs-based antiviral therapy for 12–24 weeks according to the current literature data could be suggested for patients with mild severity of renal disease without life-threatening complications, while combination therapy of rituximab plus DAAs-based regimen might be recommended in more severe cases without or without plasmapheresis when rapid control of the disease is needed [44, 48, 49].

12.5 Conclusions

IFN and RBV free DAA regimens now offer the opportunity to treat effectively and safely CHC patients with severe renal dysfunction or KT. All currently available DAAs, except for sofosbuvir and its co-formulations, can be given in CHC patients without dose modification irrespectively of baseline eGFR. The combination of glecaprevir/pibrentasvir represents a first-line pangenotypic treatment option in CHC with severe renal dysfunction including those under HD. The fixed combination of elbasvir/grazoprevir (without RBV) for 12 weeks is considered as another good option for CHC patients with genotype 1 or 4 and severe renal dysfunction. In contrast to those with GFR $>$ 30 mL/min, no prolongation of elbasvir/grazoprevir therapy or RBV coadministration are required in CHC patients with genotype 1a or 4 and GFR $\leq$ 30 mL/min possibly due to the higher accumulation of antiviral agents and the lower baseline HCV RNA levels in such cases. The 3D/2D combinations were considered to be an acceptable alternative for genotype 1b but even 1a and 4 patients, at least in areas without access to glecaprevir/pibrentasvir or at least elbasvir/grazoprevir (Table 12.4).

Table 12.4 Recommended regimens from the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) for patients with chronic hepatitis C and severe renal impairment (glomerular filtration rate < 30 mL/min)

HCV genotype	AASLD recommended regimen	EASL recommended regimen[b]
1	Elbasvir/Grazoprevir for 12 weeks (for 1a or 1b) or Glecaprevir/Pibrentasvir for 8–16 weeks[a]	Elbasvir/Grazoprevir for 12 w or Ombitasvir/Paritaprevir plus Dasabuvir for 12w (plus RBV 200 mg/d for 1a if the hemoglobin level is >10 g/dl at baseline)
2, 3, 5 or 6	Glecaprevir/Pibrentasvir for 8–16 weeks[a]	Sofosbuvir/velpatasvir or Sofosbuvir plus daclatasvir (plus ribavirin if the hemoglobin level is >10 g/dl at baseline for genotype 3) For 12 weeks (or for 24 weeks without ribavirin for genotype 3)[c]
4	Elbasvir/Grazoprevir for 12 weeks or Glecaprevir/Pibrentasvir for 8–16 weeks[a]	Elbasvir/Grazoprevir for 12 w or Ombitasvir/Paritaprevir plus Dasabuvir plus ribavirin (if the hemoglobin level is >10 g/dl at baseline) for 12 w

[a]Patients in this group should be treated as patients without CKD. Duration of glecaprevir/pibrentasvir should be based on the presence of cirrhosis and prior treatment experience

[b]According to EASL guidelines: (1) antiviral therapy is indicated in those without an indication for kidney transplantation otherwise after kidney transplantation may be preferred, and (2) sofosbuvir should be used with caution (no dose recommendation can currently be given for these patients) and with careful monitoring of renal function; (3) Ribavirin should be discontinued when severe anemia (hemoglobin <8.5 g/dL)

[c]If treatment is urgently needed or with end-stage renal disease on hemodialysis without an indication for kidney transplantation

Sofosbuvir is the only DAA with renal clearance and thus should not be given in patients with eGFR <30 mL/min or ESRD, while there have been reports implying that it might be nephrotoxic, particularly in high-risk patients, such as those with decompensated cirrhosis and LT recipients under calcineurin inhibitors. Regardless of the potential of sofosbuvir related toxicity in patients with severe renal impairment, which seems to be minimal, if any, careful renal monitoring seems to be reasonable at high renal risk patients receiving sofosbuvir-based regimens. Sofosbuvir-based regimens and particularly sofosbuvir/velpatasvir (plus RBV in subgroups of genotype 3 patients if hemoglobin level is >10 g/dL) may be still used in CHC patients with non-1, non-4 genotype, advanced liver disease, and CKD if glecaprevir/pibrentasvir is not available.

Although the literature data are scarce in the KT setting, theoretically any IFN-free DAAs regimen can be given to KT recipients with GFR ≥30 mL/min, according to the general guidelines and after taking into consideration the potential drug–drug interactions with other co-medications including the immunosuppressive agents (Table 12.1).

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Management of Hepatitis C Viral Infection in People Who Inject Drugs

13

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13.1 Prevalence of HCV Infection in People Who Inject Drugs

Drug abuse is a global health problem. In 2015, an estimated quarter of a billion people or 5% of the global adult population used drugs at least once [1]. Around 18 million people suffer from opioid addiction, the most harmful drug type in health terms, and almost 12 million people face the most severe health consequences as active injecting drug users [1]. As hepatitis C viral infection (HCV) is a blood-borne pathogen, viral transmission as a consequence of illicit drug use is a major risk factor. In Western countries, it is the most important cause of infection, and people who inject drugs (PWID) or who have ever injected drugs are the main affected group by HCV infection [2–5]. It is estimated that about 6–8 million recent PWID have chronic HCV infection, with an additional large but unquantified reservoir of infection among people who have ceased injecting [1, 6]. However, in Europe most countries lack reliable estimates of the population currently at risk for HCV infection due to injecting drug use. Based on the available data, the highest absolute numbers of current injectors are reported in the United Kingdom (122,900), the Czech Republic (45,600), Finland (15,600), Portugal (14,400), Latvia (12,600), and Spain (9900) [7]. HCV antibody (HCV Ab) prevalence in PWID is approximately 50 times higher than in the general population and ranges from 15 to 84% [8]. As for the prevalence of HCV infection in the general population, the highest estimates of HCV are present in Southern and especially Eastern Europe [6, 8–15].

Furthermore, the seroprevalence of HCV varies not only between but also within countries [16]. The seroprevalence is higher in cities than in rural areas, but there are also differences in prevalence between cities [17, 18]. This can be partly explained

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by population's age differences, but variations in profiles and practices are equally important. In France nearly one-third of injectors declared having had difficulties to obtain syringes in the 6 previous months, with clear disparities between areas [17]. Especially new injectors, with recent benzodiazepine or poly-drug abuse, are at high risk of HCV seroconversion [19–23]. High levels of injection risk behavior are associated to younger age, amphetamine use, homelessness, and female gender [24, 25].

The genotype distribution is different between PWID and the general population [26]. The most important difference is the higher prevalence of genotype 1a and 3, who are still more difficult to treat, even in the direct-acting antiviral (DAA) therapy era. Globally, the most important genotype causing HCV infection in PWID is genotype 1, but genotype 3 is also highly prevalent in PWID. Genotype 4 is most prevalent in Africa, spreading into Europe, whereas genotypes 2 and 6 are more frequent in Asia.

Co-infection with HIV ranges from 0 to 70% in HCV-infected PWID, with a median of 3.9% [5]. The rate of HIV co-infection differs greatly across Europe and is correlated to the prevalence of HIV within PWID (from 0 to 30%). This range is even wider in HCV-infected PWID, as this is a high-risk group [7].

13.2 Natural History of HCV Infection in People Who Inject Drugs

People who inject drugs have a higher standardized mortality rate than the general population [27, 28]. This high mortality rate is mostly dependent on HIV-related death or drug-related death (overdose) [27]. However, HCV infection influences this high mortality rate as well. PWID with a HCV infection have a higher overall mortality rate than PWID without a HCV infection [29]. This can only partially be explained by high-risk behavior. Starting from the age of 50 years, liver-related diseases also become a major cause of death [29, 30]. Multi-substance abuse with alcohol dependency increases the risk of end-stage liver disease significantly [31]. In a more recent investigation, the most important causes of death were drug overdose and disorder (19.8%), cardiovascular diseases (17.4%), cancer (16.8%), and infectious diseases (13.5%, including 12% HCV) [28]. HCV and alcohol use disorder were two clinically important indicators of overall mortality risk. Tobacco use disorder was associated with increased risk of cardiovascular death, HCV infection with cancer mortality risk, and HCV and alcohol use disorder with liver-related mortality risk.

13.3 Prevention of HCV Infection in People Who Inject Drugs

HCV is transmitted in illicit drug users not only by the use of non-sterile needles but also by the shared use of drug cookers, filtration cottons, and rinse water [32]. HCV incidence remains high, and PWID are the most important risk group with ongoing

transmission of HCV infection [33]. In the European Union, harm reduction policies form an integrated part of the public health response to drug use-related health problems. All countries implement opioid substitution treatment (OST) and needle and syringe programs (NSP) as core measures for the prevention and control of infections among people who inject drugs [7, 34, 35]. This is based on findings that combined OST and high-coverage NSP can reduce HCV incidence by up to 80% [36–40]. Nevertheless, HCV incidence remains high in many settings, particularly in the first several years after start of injection drug use [5, 23, 33, 41]. To influence the transmission risk, a scale-up of OST and NSP coverage is still urgently needed, as global coverage of OST and NSP programs remains low [42]. Especially in prisons, there is a lack of sufficient harm reduction measures [43, 44].

Since there is no HCV vaccine available or readily foreseeable, HCV elimination can only be obtained by treatment. Mathematical modeling studies suggest that HCV treatment can lead to substantial reductions in HCV prevalence and transmission, especially when combined with OST and NSP [45–47]. Furthermore, both interferon-based and interferon-free HCV treatments among PWID are cost-effective [48, 49]. Therefore, international guidelines state that PWID are a high priority for treatment [50–54]. Nonetheless, in order to have an effect of therapy on the population level, targeted interventions to enhance screening, linkage to care, and treatment are needed [53].

Also vaccination for HBV is advocated in PWID [53]. However, in drug users tested for HBV markers, at their first access to public addiction clinics in the metropolitan area of Bologna, Italy, born after 1981, and so eligible to have received HBV vaccination in adolescence or at birth, antibodies against HBV core antigen had a significant high prevalence of 6.2% [55]. An accelerated vaccination schedule should be considered in drug users with low adherence. Drug users in the accelerated schedule group (0–1–2 months) had significantly lower HBV infection rates but had a similar rate of anti-HB antibody loss compared with the standard schedule (0–1–6 months) group over 2 years of follow-up. No chronic HBV infections were observed. Hepatitis C positivity at enrollment and age younger than 40 years were independent risk factors for HBV infection and antibody loss, respectively [56].

13.4 Screening for HCV Infection in People Who Inject Drugs

The disease burden of HCV infection is high. Furthermore, without treatment, an increase in the occurrence of decompensated cirrhosis and hepatocellular carcinoma is expected in the next decade [57, 58]. Because of a high prevalence and low rate of diagnosis and an early asymptomatic period, chronic hepatitis C viral infection is an ideal condition for preventive screening [59]. Furthermore, the economic evidence for screening high-risk populations is robust. If a cost per quality-adjusted life-year (QALY) of £30,000 is considered reasonable value for money, then screening birth cohorts, drug users, and other high-risk populations are policy options that should be considered according to a recent systematic review [60]. Therefore, all injecting drug users (current or ever, including those who injected once), intranasal illicit drug

Table 13.1 Benefits and risks of dried blood spot testing and point-of-care testing

	Dried blood spot testing	Point-of-care testing
Benefits	1-step diagnosis: reflex testing can be implemented with HCV confirmation on the same filter	Immediate result of testing, no need for referral
	No need of phlebotomy	Immediate education and linkage to care
	Stable and easy to transport once dried	
Risks	Referral to centralized laboratory, patient needs to return for result	HCV Ab test only at this point, so second test with phlebotomy still necessary

users, and persons who were ever incarcerated should be screened for HCV infection at least once in their lifetime [50–52].

Nevertheless, globally HCV testing and diagnosis are still inadequate [61–65]. There are several potential strategies to improve HCV testing: education and counseling by health professionals with on-site testing [66–71], electronic health record reminders to increase targeted risk-based testing [67, 71–74], and simplification of testing such as dried blood spot testing [67, 71, 75–80] and point-of-care HCV testing [81–85]. The benefits and risks are listed in Table 13.1. Both dried blood spot testing and point-of-care testing avoid the need for phlebotomy, which is often a barrier to testing in PWID with poor venous access [86, 87]. In contrast, finger prick testing has been shown to be widely acceptable [88].

As more people will get cured from their HCV infection, and there is a spontaneous cure rate of 25%, screening for HCV RNA will be necessary, especially in this high-risk group with a high prevalence of HCV Ab positivity. Novel point-of care tests, such as the Xpert HCV Viral Load test, are currently under development. In the first trial, good sensitivity and specificity were obtained for detection of HCV viral RNA in finger-stick samples, but these results need to be validated [84, 89]. Furthermore, simplified HCV diagnosis can also be made using HCV core antigen, which could be used as an alternative to HCV RNA in low- and middle-income countries or high prevalence settings such as PWID [90–93]. In the future, a low-cost, rapid (<60 min) point-of-care test is needed to facilitate linkage to HCV care in a single visit [85]. Genotyping can be performed at the clinic when a treatment assessment is performed, and with future regimens, this might not be necessary anymore [94, 95].

13.5 HCV Infection Treatment in People Who Inject Drugs

Although acceptable outcome in substance users in comparison with non-substance users, there were many barriers to treatment for PWID in the interferon era [96, 97]. A major problem was the occurrence of mental health conditions among PWID. Psychosis was a known side effect of interferon, and as such many PWID were denied treatment [98–101]. Concerns about treatment adherence and the long treatment duration, with many side effects, influenced the treatment uptake. Today,

thanks to the availability of direct-acting antiviral therapy (DAA), these barriers are lifted. DAAs have limited side effects, and the shorter treatment duration is also a potential benefit that can increase treatment uptake and adherence in PWID. A potential problem with DAA therapy was drug-drug interactions, but data from several prospective trials have shown no influence of methadone or active drug use on the outcome in PWID [102–105]. Thus methadone and buprenorphine are safe and effective in combination with DAA therapy. Furthermore, these studies also demonstrated high rates of viral eradication in active drug users on OST, non-inferior to the results in the general population. Real-life studies confirm these high viral eradication rates in substance abusers, both in the setting of patients stable on OST and even in patients with recent HCV exposure due to active drug use [106–112]. Furthermore, although good adherence is necessary to minimize the risk of treatment failure and viral resistance, SVR seems to be possible even with a few missed doses [108]. In the study of Mason et al., the only factor influencing treatment adherence in multivariate analysis was moderate to heavy alcohol use. Active drug abuse did not influence treatment adherence, and overall outcome (SVR) was excellent. Thus the importance of adherence should be stated by the treating physician when starting antiviral therapy, but concerns about the lack of treatment adherence should not be considered as a barrier to treat PWID anymore.

As such there is currently sufficient evidence that PWID can be cured from HCV infection as effective and safe as non-PWID. However, the importance of treating PWID lies not only in the possibility of eliminating the virus in individual patients and at the population level [54, 102–105, 113, 114]. Treatment of HCV infection with SVR also leads to a reduction in mortality [115]. Furthermore, it can lead to a psychological transformation (reduced stigma and shame, enhanced self-esteem, self-care, and ability to disclose), to behavioral change with healthier lifestyles (reduction in unsafe injection practices, cessation of drug and alcohol use), and to a social transformation (improved housing, employment, education, and enhanced altruism) [116–118].

13.6 Barriers to Treatment for HCV Infection in People Who Inject Drugs

Despite the fact that PWID can be cured from HCV infection, with substantial additional benefits that could arise, uptake for therapy remains low. Cumulative HCV treatment uptake among OST patients notified with HCV infection in Norway between 2004 and 2013 was 14%. Annual treatment rates during OST remained unchanged below 3% per year.

To reduce the transmission rate at the population level, 10% of the total PWID population should be treated annually [45, 119]. Currently, these treatment levels are not being reached. This is caused by barriers at the patient, provider, and institutional level [120].

At the patient level, mostly stable patients on OST are being reached for screening and treatment. In a Norwegian study, high continuity of OST over time and absence

of substantial benzodiazepine use predicted HCV treatment uptake [121]. In another trial, patients who were African, used drugs, smoked, and used alcohol were less likely to receive HCV treatment [122]. Moreover, access to HCV antiviral therapies remains limited due to the under-diagnosis of infection in PWID [123].

At the provider level, stigmata concerning lack of treatment adherence, high costs of treatment, and the risk of reinfection still influence the uptake for treatment for PWID [124]. These misunderstandings should be addressed as they lead to frustration for patients and loss of confidence in the medical system. Furthermore, there is a lack of training of general physicians (GPs). The GPs' decision to offer screening to risk groups often seems to be an individual choice of the healthcare professional. Raising GPs' awareness of the disease, for example, through the adoption of effective strategies for the dissemination and implementation of the existing guidelines for general practice, is strongly needed. The role of GPs and specialists involved in the management of chronically infected patients should also be clarified, as opinions sometimes differ markedly even within each professional group [125].

At the institutional level, policy decisions have created new artificial barriers: restrictions on therapy based on the presence of active substance and/or alcohol abuse and restrictions based on fibrosis levels so that only patients with a late-stage liver disease can be treated [126–129]. In Europe, there remain a lot of DAA reimbursement restrictions and disparities: In relation to substance use, 15% of the European countries require abstinence of substance use prior to treatment. Only 21% of the European countries have no fibrosis reimbursement restrictions. In several countries (e.g., Belgium, Croatia, Czech Republic), HIV/HCV co-infected persons have fewer restrictions than HCV mono-infected [129]. In the United States, the high costs of HCV DAA therapy have resulted in the implementation of onerous requirements to obtain approval for treatment [126–128, 130, 131]. In some cases, 6 months of documented abstinence from illicit substance use or excessive alcohol intake, in addition to enrollment in a formal substance use treatment program, may be mandated. Additional requirements may include written informed consent stipulating that patients will be adherent to the therapeutic regimen.

13.7 Addressing Barriers to Care of HCV Infection in People Who Inject Drugs

To eliminate the virus, major efforts will have to be made to reach out to the more marginalized patients and active substance users. Excellent results were obtained by taking the screening and therapy outside of the hospitals directly to the patients with the use of mobile screening and treatment teams in France [132]. Feasibility and cost-effectiveness of outreach testing and treatment of hepatitis C were demonstrated within comparable drug treatment settings. Furthermore, the cost of newer DAA therapies would not be prohibitive when considering willingness-to-pay thresholds commonly used by policy-makers [133]. Also, enhanced patient navigation models (case management, multidisciplinary treatment under one roof) can increase uptake for treatment significantly [87, 134–136]. Finally, in a randomized controlled trial,

the use of peers was significantly more successful to retain patients in care than using cash incentives or the usual care [137]. These efforts are worthwhile as increased access to treatment brings substantial value to society. Over the long term, it reduces cost for payers as the benefits acquired from a reduction in prevalent and incident cases, mortality, and medical costs due to hospitalization for end-stage liver disease or HCC outweigh the cost of treatment [49, 123, 138]. In the following paragraphs, the different models will be discussed in detail.

13.7.1 Models of HCV Treatment Delivery to People Who Inject Drugs

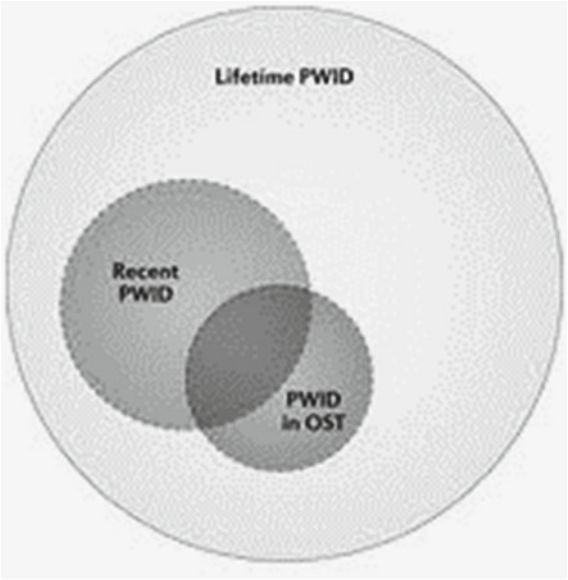
Multidisciplinary programs offering primary care, behavioral medicine, and social services are better equipped to engage PWID in HCV care [139]. Therefore, PWID in different stages of treatment, with different availability of services, will experience different obstacles for HCV linkage to care and treatment. To improve uptake for treatment for HCV infection in PWID, efforts to provide outreach and deliver integrated care at the OST clinics, NSP, detoxification centers, and/or correctional facilities are urgently needed. This is critical to have a greater impact on the prevalence of HCV infection. Numerous interventions have been used to link PWID to HCV treatment. Most of them fall into two categories: referral to a liver or infectious disease specialist or integrated care for HCV infection at the OST centers [126] (Fig. 13.1).

13.7.1.1 Referral for HCV Care

Referral is the most frequently used strategy to treat PWID for HCV infection. However, this could be a barrier to care, as PWID mistrust the healthcare system or they encounter stigmatization at the conventional healthcare settings. Especially if there is a large distance between centers, less than one-third appear at the specialty clinics for appointments, and $<20\%$ of those evaluated actually started treatment [140–143]. However, these studies were conducted in the interferon era. Recently, higher referral rates and treatment uptake of more than 60% (if not for reimbursement criteria) were obtained in the DAA treatment era [87].

13.7.1.2 Integrated Care

Colocalization of substance abuse treatment and HCV treatment increases the uptake for HCV evaluation [144–147]. Since there are multiple settings to provide substance use treatment, a wide variety of integrated medical care models have been developed [148]. These care models consist of the multidisciplinary team with psychologists, addiction care physicians, psychiatrists, and peer support, necessary to treat substance abuse, in combination with members of diverse healthcare specialties to treat diverse medical issues. A multidisciplinary care model located at the OST setting facilities was extremely effective [149]. Also in community health centers, at the hepatitis clinics, and in general medical practices, the implementation of colocalized care has been successful [150–154]. These models have further



Adapted from Grebely et al. 2015,
nature reviews gastroenterology and hepatology

Fig. 13.1 There is a wide variety in the substance use paradigm. PWID include active users who continue to inject; those in early recovery, typically on OST; and lifetime PWID who may or may not receive treatment for addiction (see Fig. 13.1). Furthermore, there is a heterogeneity in terms of different types of drug use, frequency, and engagement in the healthcare system [126]. The frequency of drug use can range from daily to periods of abstinence with continuous risk of relapse. The level of services provided to PWID in recovery often determines the engagement in HCV management. (Adapted from Grebely et al. 2015, nature reviews gastroenterology and hepatology)

benefits as they can incorporate peer models or (modified) directly observed therapy to improve treatment uptake, adherence, and outcome even more [155–157].

13.7.1.3 Virtual Integration

Especially in regions where there are large distances between clinics, and there is a lack of infrastructure to treat HCV infection (lack of hepatology specialists or infectious disease specialists), the use of telehealth can increase the uptake for treatment [154]. Telehealth is a convenient way to train addiction physicians or general physicians to treat HCV infection, which increases the treatment facilities substantially. In the DAA era, with the availability of well-tolerated, highly effective treatments, this could be an effective way to treat PWID. Whereas in this telemedicine approach, communication is used to train physicians, another approach is to use telehealth. With telehealth, there is a synchronous interaction between patient and physician. In a pilot study, collocating a telemedicine-based HCV treatment program in the OST facility resulted in high levels of patient satisfaction and treatment

adherence [158]. However, infrastructural limitations and lack of broadband connectivity could limit these results.

13.7.2 Support Services to Promote the Engagement of People Who Inject Drugs for Hepatitis C Care

PWID often lack knowledge about HCV infection. Besides that, they often have coexisting economical and psychosocial difficulties. Therefore, a combination of additional efforts such as educational programs and medical interventions with behavioral components is necessary to increase the uptake for HCV care [67, 126, 148].

13.7.2.1 Educational Support

HCV-related education increases patient engagement into HCV care [159]. Regular educational interactions delivered by physicians or other healthcare personnel can promote treatment adherence, but other important topics are screening for HCV infection, the long-term complications of chronic infection, and the availability of well-tolerated, highly effective therapy. Educational programs might also specifically target active injectors, promote harm reduction, and facilitate entrance for PWID into multidisciplinary programs for treatment of both substance use and HCV infection. Patients' knowledge about HCV infection is found to be significantly improved after a comprehensive and interactive hepatitis C-related educational intervention, composed of two 30- to 60-min sessions conducted during 2 consecutive weeks [160, 161].

13.7.2.2 Case Management

Case management is defined and published in the Case Management Society of America (CMSA) Standards of Practice for Case Management as a collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available resources to promote quality cost-effective outcomes. The philosophy of case management is that all individuals are eligible for case management services regardless of age, culture, or ability to pay for service [162]. For case management to succeed, early risk identification, using proven indicators, and the stratification of the group according to these indicators are critical so that appropriate interventions and resources are utilized. Case management is a voluntary service, so gaining permission from, and establishing trust with, the patient, family, and caregivers is critical. To achieve positive outcomes, the cooperation of the patient, family, and caregiver is needed to ensure adherence with the plan of care. Today, a key aspect of effective case management is the ability to assess an individual's knowledge, motivation, and attitude toward care in order to influence adherence.

As PWID may face limited economic and social support, case management may play a central role in the coordination of care within a complex healthcare system and

could facilitate HCV screening as well as linkage to care. Case management could also be instrumental in the acquisition of HCV medications for PWID through providing assistance with obtaining health insurance and enrollment in medication reimbursement programs. Once antiviral therapy is initiated, case managers can also provide guidance with maintaining adherence to the treatment regimen and consistent follow-up with provider appointments. Today, case management is mostly used in the chronic care setting in the United States, but it has also been tested in the HIV setting [163, 164]. Furthermore, Masson et al. provided case management services in the HCV setting and improved the likelihood for treatment referral to an HCV clinic by a 4:1 ratio in a randomized controlled trial [165]. Thus, case management should be implemented to improve HCV care for PWID.

13.7.2.3 Patient and Peer Navigation

By guiding patients through the healthcare system, initiation, linkage, and retention in medical care are improved. Peer navigation is provided by other patients who often have passed through the same healthcare trajectory. Both patient and peer navigations aim to ensure patients receive standard of care in a timely manner [166]. Navigators focus exclusively on healthcare processes, and this task can be part of the responsibility of case managers [167]. Nevertheless, patient navigation alone also improves the access to care, adherence to therapy, and the sense of independence of patients. It reduces social isolation, improves quality of care, and increases patient satisfaction [168, 169]. As it is mostly performed by lay people, cost is significantly lower than other interventions. Furthermore, it can lead to cost reduction in terms of fewer hospitalizations [170]. When targeted to patient groups who are not highly engaged in medical care due to (perceived) barriers, it is most effective [167, 170, 171].

The organization of patient navigation by peers has additional benefits in the areas of substance use, treatment engagement, HIV/HCV risk behaviors, and secondary substance-related behaviors such as craving and self-efficacy. However, limitations are noted on the relative lack of rigorously tested empirical studies within the literature and inability to disentangle the effects of the group treatment that is often included as a component of other services [135, 172]. When compared to cash incentives, the use of peers was slightly better to increase uptake for treatment and adherence to care, but not statistically significant [137].

13.8 Follow-Up of PWID Following HCV Cure

One of the most important barriers to care is the risk for reinfection after cure, which was often cited by physicians as a reason to withhold PWID from treatment. The high cost of DAA therapy increased this barrier even more. However, due to the high success rates of DAA therapy, viral elimination is a possibility [173, 174]. Therefore, reinfection should not be a concern. On the contrary, a rapid scale-up is needed to reduce the viremic pool [175]. Nevertheless, reinfection will occur, and follow-up with yearly HCV RNA testing is necessary.

Ongoing risk behaviors following successful HCV therapy and lack of adequate coverage of harm reduction interventions (NSP and OST) increase rates of reinfection and compromise treatment outcomes [116, 176]. The incidence of HCV reinfection following successful interferon-based treatment among PWID ranges from 0.0 to 5.3/100 person years [176–182]. These differences are explained by a heterogeneity in study populations with regard to sample size, risk behavior definitions, study designs, and applied virologic methods [176, 177]. In a recent study of HIV/HCV co-infected PWID, the greatest risk of reinfection was by high frequency injection drug use (cocaine and methamphetamines) [182]. The pooled estimate of reinfection was 2.2/100 person years (95% CI, 0.9–6.1) overall and 6.4/100 person years (95% CI, 2.5–16.7) among individuals who reported injection drug use after treatment-induced HCV clearance [178]. In a further meta-analysis in settings of interferon-based therapy, the HCV reinfection rate was 0.0 per 100 person years (95% CI, 0.0–0.0) in "low-risk" populations with HCV mono-infection, 1.9 (1.1–2.8) per 100 person years in PWID or prisoners with HCV mono-infection, and 3.2 (0.0–12.3) per 100 person years in those with HIV/HCV co-infection [180]. In the only study of reinfection post-DAA therapy, spontaneous clearance of HCV reinfection was observed in three of six cases, suggesting some degree of partial immunity against reinfection [183]. Thus reinfection will occur, but probably in a lower percentage of the PWID than previously feared, especially with rapid scale-up of treatment. To further prevent reinfection, the "bring your friend" strategy can reduce the viremic pool in direct contacts of the treated patient [46]. Discussing the risk of reinfection, providing high coverage of harm reduction, yearly monitoring, and retreating patients if necessary will be the strategy to eliminate HCV [40].

Finally, in patients with severe fibrosis (F3-F4 METAVIR score), continued monitoring for hepatocellular carcinoma (HCC) is necessary. Cancer risk persists even after 10 years of viral cure, and thus a clinical strategy for its monitoring is needed. Several risk-predictive host factors, e.g., advanced liver fibrosis, older age, accompanying metabolic diseases such as diabetes, persisting hepatic inflammation, and elevated alpha-fetoprotein, as well as viral factors, e.g., core protein variants and genotype 3, have been reported [123]. There is no increased risk of HCC after DAA therapy, but monitoring remains necessary in high-risk patients [184–186]. Especially not reaching SVR had a significant impact on the HCC progression rate in patients treated with DAA on the transplant list; no direct effect of DAA was observed [186]. Importantly, only 80% of the patients in a real-life cohort were screened sufficiently for HCC before start of DAA therapy [184]. Surveillance for HCC by ultrasonography and alfa-fetoprotein testing every 6 months is necessary in all patients with severe fibrosis, and more awareness is necessary to keep PWID in follow-up, also after successful DAA therapy.

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Patient-Reported Outcomes in Hepatitis C Infection

14

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Hepatitis C virus infection (HCV) affects approximately 71 million individuals globally. HCV is self-limiting in 15–45% of infected persons who spontaneously clear the virus within 6 months of infection without any treatment. The remaining 60–80% of persons will develop chronic HCV infection (C-HC). Of those with chronic HCV infection, the risk of cirrhosis of the liver is between 15 and 30% within 20 years and is the most common cause of cirrhosis and its complications (hepatocellular carcinoma) in the United States and the Western world. C-HC is associated with increased mortality, resource utilization, and impairment of patients' well-being [1–6].

14.1 Health-Related Quality of Life (HRQL)

Patient-reported outcomes (PROs) are surrogates of patient experience. In fact, PRO is defined as a direct report by the patient (without modification by anyone) that pertains to his or her health, quality of life, or functional status association with health care or treatment. One of the most important PROs is HRQL [7].

Over a decade ago, a meta-analytic assessment of patients with HCV infection suggested a significant impairment of health-related quality of life of HCV-infected patients even before reaching the stage of cirrhosis [8]. In fact, other studies suggested HRQL in HCV patients is driven by fatigue and psychological issues,

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most notably depression and cognitive impairment, which often leads to stigmatization becoming a barrier to treatment and eroding a patient's social support network [9–12]. In addition to physical and psychiatric comorbidities, active viremia has also been suspected to further impair HRQL and other PROs [10].

In a recent HCV HRQL meta-analysis, investigators found that patients experienced significant impairment in their mental health domain and reported significant fatigue [13]. These are important findings as impaired HRQL and fatigue have been found to have a negative impact on worker productivity estimated to cost the United States $8352 per year per HCV-infected patient [14]. In 2011, the total economic burden of HCV-related liver disease in the United States was estimated to be 6.1 billion dollars annually [15].

14.2 HRQL Measurement Tools

Since HCV creates a significant impairment in patient-reported outcomes, it is imperative to understand the realm of patient-reported outcomes and the tools that are used to measure patient-reported outcomes in patients with CHC. A widely used definition of patient-reported outcomes is the definition from the National Quality Forum and the Centers for Disease Control and Prevention which reads, "Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [7, 16]. Currently, the tools used to measure PROs can be divided into three categories: health-related quality of life, fatigue, and work productivity with the majority of research uses four measurement tools which include Short Form-36 version 2 (SF-36v2), the Chronic Liver Disease Questionnaire (CLDQ) with specific versions for hepatitis C virus (CLDQ-HCV), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Work Productivity and Activity Impairment—Specific Health Problem (WPAI:SHP) tools [17–21].

The SF-36v2 is a widely used instrument for HRQL evaluation. It assesses eight HRQL scales (ranging 0–100 with higher values corresponding to a better health status): physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The two summary scores summarize the physical and mental health components of SF-36: the Physical Component Summary (PCS) score and Mental Component Summary (MCS) score [17].

The CLDQ includes four HRQL scales: activity and energy (AE), emotional (EM), worry (WO), and systemic (SY). These scales are averaged to the total CLDQ-HCV score that ranges 1–7 with higher values representing better HRQL. The CLDQ-HCV tool is a validated HRQL instrument developed specifically for assessment of HRQL in HCV patients [18, 19].

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a widely used and extensively validated 40-item PRO questionnaire that assesses fatigue and its impact upon daily activities. The scoring scheme includes physical (PWB), emotional (EWB), social (SWB), and functional (FWB) well-being domains

as well as the fatigue subscale domain (FS); these five scales together add up to the total FACIT-F score that ranges 0–160 with higher values representing better well-being [20].

Finally, the WPAI:SHP questionnaire is another validated PRO instrument where participants are asked to evaluate impairment in their daily activities and work productivity associated with a specific health problem, and for patients with liver disease, patients are asked to think about how their disease state impacts their life. Specifically, in the WPAI:SHP, the work impairment domain is a sum of impairment in work productivity due to absenteeism and impairment due to decreased productivity while working (presenteeism); this domain is assessed only in those who report being employed at the time of completing the questionnaire. The activity impairment domain represents impairment in daily activities other than work and is assessed in all participants regardless of their employment status. Higher impairment scores indicate poorer health status: the minimum possible value of 0 represents no impairment in work productivity or daily activities, while the value of 1 represents complete inability to work or perform those activities [21].

14.3 Impact of Treatment on HCV PROs

Until recently, treatment of CH-C contained interferon-based regimens with relatively low efficacy, substantial side effects, and negative impact on patients' well-being [22, 23]. Nevertheless, these early studies have suggested that achieving a sustained virologic response (SVR), even with interferon-based treatment (i.e., being HCV RNA negative 6 months after completing therapy), can be associated with an increase in HRQL scores [22, 23]. In this context, it is important to determine the minimally important difference (MCID) of most HRQL domains for patients with HCV. Although still debated, MCID in the context of CHC has been established to between 5 and 10% [24].

In order to place the impact of different treatment regimens, a recent study compared PRO changes during treatment with interferon (IFN)-based treatment to IFN-free treatments using the new direct-acting antiviral agents. The study reported that during treatment, patients receiving IFN experienced substantial impairment in their PROs when measured with the SF-36, CLDQ-HCV, FACIT-F, and WPAI:SHP (up to −24.4% by treatment week 12, up to −8.3% at week 4 post-treatment). In contrast, patients receiving IFN-free and ribavirin (RBV)-containing regimens experienced smaller PRO impairments (up to −7.1% by treatment week 12) which returned to baseline or improved by post-treatment week 4. Furthermore, patients receiving IFN- and RBV-free regimens experienced improvement of their PROs during treatment. Finally, achieving SVR-12 was associated with improvement of PRO scores regardless of the regimen (up to +7.1%, $p < 0.0001$) or previous treatment experience. In multivariate analysis, the use of IFN was independently associated with lower PROs [25].

In addition, a number of other clinical trials have incorporated PROs while using IFN- and RBV-free regimens. Again, regardless of treatment, all those who reached

SVR-12 experienced significant increases in most domains of all tools with the majority of the increases reaching the MCID. The one domain not adversely or positively affected by treatment was the absenteeism of the WPAI:SHP. It is possible that despite higher absenteeism in HCV patients, many of these patients continue to work in order to maintain their health insurance at least in the United States so many do not miss work [26]. It is interesting to note that PRO improvement with SVR has been documented with patient population from the United States, European countries, as well as Asian countries [27–29]. This suggests that viral eradication can have a universal benefit for PROs across the globe [26].

In the context of PROs, it is important to mention a number of special patient populations. First, patient with minimal or no fibrosis did improve their PRO score. This suggests that stage of liver disease should not be a prerequisite for HCV treatment [30, 31]. Nevertheless, the data also show that patients with cirrhosis, especially those with decompensated cirrhosis, experience substantial gains in PROs after achieving SVR [32]. Another group of patients who experience improvement of PROs with SVR are HIV-HCV co-infected patients. In this context, similar to their clinical data, these patients should not be distinguished from mono-infected patients regarding their candidacy for treatment [33]. Furthermore, children and adolescent who are treated for HCV and achieve SVR also improve their PROs [34, 35]. Finally, elderly patients treated with the new regimens who achieve SVR also enjoy improvement of PROs [36]. In all of these studies, it has become clear that comorbidities (psychological such as depression and anxiety and physical such as diabetes) and viremia are the main drivers of PRO impairment. Although PRO improvements can occur post-SVR, the residual PRO impairment is primarily explained by comorbidities [37]. Finally, recent data suggest that improvement of PROs post-SVR is sustainable at least 3 years post-treatment [38].

Although most of PRO data have originated from clinical trials, recent real-world PRO evidence suggests similar results [39]. Nevertheless, more studies of real-world PRO data are needed.

14.4 Importance of PROS in C-HC

Patient-reported outcomes can have a number of important implications. First, in the context of assessing the total burden of HCV infection, it is important to assess clinical and economic burden, as well as PRO burden. Second, when assessing the efficacy and effectiveness of a new regimen, the comprehensive impact of the drug must be assessed. This requires assessment of clinical outcomes such as SVR, but also patient-reported outcomes. Third, PROs such as fatigue can be driver of work productivity of patients with HCV infection. By assessing PROs, we can assess the indirect economic burden of HCV to the society. Finally, assessment of PROs in clinical practice can provide a window into the experience of patients with their disease. This can be monitored during clinical base to assess not only the progress of a patient but also the prognosis of these patients. In fact, PROs can be independent predictor of mortality in patients with liver disease [40]. Finally, inclusion of PRO

data will help with health policies and legislation to allocate resources based on unmet needs, guide the development of strategic plans, and monitor the effectiveness of broad community interventions [41].

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