

EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver*

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide [1]. The long-term impact of HCV infection is highly variable, ranging from minimal histological changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma (HCC). The number of chronically infected persons worldwide is estimated to be about 160 million, but most are unaware of their infection. The implementation of extended criteria for screening for HCV is a subject of major debate among different stakeholders. Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, thanks to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention.

These EASL Recommendations on Treatment of Hepatitis C are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the current optimal management of patients with acute and chronic HCV infections. These recommendations apply to therapies that have been approved in the European Union at the time of their publication.

The standard of care up to 2014

The primary goal of HCV therapy is to cure the infection. A sustained virological response (SVR) is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. The infection is cured in more than 99% of patients who achieve an SVR. The SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. Recent data suggest that the risk of HCC and all-cause mortality is significantly reduced, but not eliminated, in cirrhotic patients who clear HCV compared to untreated patients and non-sustained virological responders [2,3]. HCV may also affect

neurocognition and effective viral suppression is associated with reversal of cerebral magnetic resonance abnormalities [4].

Until 2011, the combination of pegylated interferon (PegIFN)- α and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitis C [5]. With this regimen, patients infected with HCV genotype 1 had SVR rates of approximately 40% in North America and 50% in Western Europe. Higher SVR rates were achieved in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%, and higher for genotype 2 than for genotypes 3, 5, and 6) and intermediate SVR rates were achieved in those with HCV genotype 4 [6].

In 2011, telaprevir and boceprevir were licensed for use in HCV genotype 1 infection. These two drugs are first-wave, first-generation direct-acting antivirals (DAAs). Both target the HCV NS3-4A serine protease and are thus referred to as protease inhibitors. Both telaprevir and boceprevir must be administered in combination with PegIFN- α and ribavirin. In the Phase III trials of boceprevir and telaprevir in HCV genotype 1 treatment-naïve patients, triple therapy regimens achieved higher SVR rates than PegIFN- α and ribavirin dual therapy, of the order of 65% to 75% [7–10]. However, the side effect profiles of these triple combination therapies and the costs per SVR in patients with advanced hepatic fibrosis are such that they should ideally no longer be used in patients infected with HCV genotype 1, as soon as other, more efficacious and better tolerated options are available.

Three new HCV DAAs have been licensed in the EU in 2014, for use as part of combination therapies for HCV infection. Sofosbuvir, a pangenotypic nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, has been approved in January 2014. Simeprevir, a second-wave, first-generation NS3-4A protease inhibitor active against genotypes 1 and 4 has been approved in May 2014. Daclatasvir, a pangenotypic NS5A inhibitor, has been approved in August 2014.

Each of these three DAAs can be used as a component of a triple combination regimen with PegIFN- α and ribavirin, yielding SVR rates of 60–100% according to the DAA used, the HCV genotype, the presence of detectable pre-existing amino acid substitutions conferring resistance to the DAA used and the severity of liver disease. Although these combinations are better tolerated than triple combination including telaprevir or boceprevir, their side effect profiles and management remain challenging because of the use of PegIFN- α and of ribavirin.

With three new HCV DAAs approved, IFN-free combinations were broadly used across Europe in 2014, initially as part of early access programs, essentially in patients with advanced liver disease (fibrosis METAVIR score F3 or F4). The combination of sofosbuvir and ribavirin is indicated in patients infected with HCV

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genotypes 2 (12 weeks) or 3 (24 weeks), yielding SVR rates of the order of 80–95%. The IFN-free combination of sofosbuvir and simeprevir, with or without ribavirin, was used based on the results of the small-size Phase II COSMOS study in patients infected with genotype 1 who achieved SVR in 93–100% of cases [11]. Recent preliminary real-life data from the US showed SVR rates slightly below those in the COSMOS trial in patients with genotype 1 infection: 82% SVR12 in the TRIO study, 89% SVR4 in the TARGET study [12,13]. The combination of sofosbuvir and daclatasvir, with or without ribavirin, has also been widely used in patients with advanced liver disease throughout Europe, based on the results of a Phase II study in patients infected with genotype 1 reporting SVR rates between 95% and 100% [14]. This combination was well tolerated over the course of therapy in the trial, and real-life data are awaited.

The panel recognises the heterogeneity of per capita incomes and health insurance systems across Europe and in other regions, and therefore the possible necessity to continue to utilise regimens with PegIFN- α and ribavirin, with or without the first-wave, first-generation protease inhibitors telaprevir or boceprevir. However, the advent of new DAAs implies that these regimens are not recommended in 2015. It is hoped that the publication of up-to-date recommendations will guide reimbursement (and discounting of drug costs) in order to harmonize treatments across different countries and regions.

Methodology

These EASL recommendations have been prepared by a panel of experts chosen by the EASL Governing Board. The recommendations were approved by the EASL Governing Board. The recommendations have been based as far as possible on evidence from existing publications and presentations at international meetings, and, if evidence was unavailable, the experts' provide personal experiences and opinion. Where possible, the level of evidence and recommendation are cited. The evidence and recommendations have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated [15]. The quality of the evidence in the recommendations has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) or weak (2) (Table 1). The recommendations thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.

These recommendations are necessarily based on currently licensed drugs. They will be updated regularly, following approval of new drug regimens by the European Medicines Agency.

Recommendations

Diagnosis of acute and chronic hepatitis C

The diagnosis of acute and chronic HCV infection is based on the detection of HCV RNA by a sensitive molecular method (lower

limit of detection <15 international units [IU]/ml). Anti-HCV antibodies are detectable by enzyme immunoassay (EIA) in the vast majority of patients with HCV infection, but EIA results may be negative in early acute hepatitis C and in profoundly immunosuppressed patients. Following spontaneous or treatment-induced viral clearance, anti-HCV antibodies persist in the absence of HCV RNA but may decline and finally disappear in some individuals [16,17].

The diagnosis of acute hepatitis C can be confidently made only if seroconversion to anti-HCV antibodies can be documented, since there is no serological marker which proves that HCV infection is in the *de novo* acquired acute phase. Not all patients with acute hepatitis C will be anti-HCV-positive at diagnosis. In these cases, acute hepatitis C can be suspected if the clinical signs and symptoms are compatible with acute hepatitis C (alanine aminotransferase [ALT] >10 times the upper limit of normal, jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable. In all cases, HCV RNA can be detected during the acute phase although brief interludes of undetectable HCV RNA may occur.

The diagnosis of chronic hepatitis C is based on the detection of both anti-HCV antibodies and HCV RNA in the presence of biological or histological signs of chronic hepatitis. Since, in the case of a newly acquired HCV infection, spontaneous viral clearance is very rare beyond 4 to 6 months of infection, the diagnosis of chronic hepatitis C can be made after that time period.

Recommendations

- Anti-HCV antibodies are the first-line diagnostic test for HCV infection (**A1**)
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation (**A1**)
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method (**A1**)
- Anti-HCV-positive, HCV RNA negative individuals should be retested for HCV RNA three months later to confirm true convalescence (**A1**)

Screening for chronic hepatitis C

Because of the approval of highly efficacious new HCV treatment regimens, access to therapy must be broadened. A substantial proportion of patients with chronic hepatitis C are unaware of their infection. In addition, accurate HCV prevalence and incidence data are needed to analyse the magnitude of the pandemic in different regions and to design public health interventions. Thus, hepatitis C testing is required to identify infected persons and engage them in care and treatment, and targeted screening for markers of HCV infection must be implemented. Groups at higher risk of HCV infection can be identified, and should be tested. At-risk populations, that should be screened, depend on the local epidemiology of HCV infection. In addition to EIAs, rapid

Table 1. Evidence grading used (adapted from the GRADE system).

Evidence quality	Notes	Grading
High	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation	Notes	Grading
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	2

diagnostic tests (RDTs) can be used to screen for anti-HCV antibodies. RDTs use various matrices, including serum, plasma, but also fingerstick capillary whole blood or, for some of them, oral (crevicular) fluid, facilitating screening without the need for venous puncture, tube centrifugation, freezing and skilled labour. RDTs are simple to perform at room temperature without specific instrumentation or extensive training.

Recommendations

- Screening for HCV infection must be recommended in targeted populations defined according to the local epidemiology of HCV infection, ideally within the framework of national plans (**A1**)
- Screening for HCV infection must be based on the detection of anti-HCV antibodies (**A1**)
- Rapid diagnostic tests can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care (**B1**)
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method to identify patients with on-going infection (**A1**)

Goals and endpoints of HCV therapy

The goal of therapy is to cure HCV infection in order to prevent the complications of HCV-related liver and extra-hepatic diseases, including hepatic necro-inflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death.

The endpoint of therapy is an SVR, defined by undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy, as assessed by a sensitive molecular method with a lower limit of detection ≤ 15 IU/ml. Both SVR12 and SVR24 have been accepted as endpoints of therapy by regulators in the US and Europe, given that their concordance is 99% [18]. Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases [19].

Recommendations

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extra-hepatic manifestations and death (**A1**)
- The endpoint of therapy is undetectable HCV RNA in a sensitive assay (≤ 15 IU/ml) 12 weeks (SVR12) and 24 weeks (SVR24) after the end of treatment (**A1**)
- In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients surveillance for HCC should be continued (**A1**)
- In patients with decompensated cirrhosis, HCV eradication reduces the need for liver transplantation. Whether HCV eradication impacts mid- to long-term survival in these patients is unknown (**B2**)

Pre-therapeutic assessment

The causal relationship between HCV infection and liver disease should be established, liver disease severity must be assessed, and baseline virological parameters that will be useful for tailoring therapy should be determined.

Search for other causes of liver disease

Other causes of chronic liver disease, or factors which are likely to affect the natural history or progression of liver disease, should be systematically investigated and all patients should be tested for other hepatotropic viruses, particularly hepatitis B virus (HBV), and for human immunodeficiency virus (HIV). Alcohol consumption should be assessed and quantified, and specific counselling to stop any use of alcohol should be given. Possible comorbidities, including alcoholism, autoimmunity, genetic or metabolic liver diseases (for instance genetic hemochromatosis, diabetes or obesity) and the possibility of drug-induced hepatotoxicity should be assessed.

Assessment of liver disease severity

Assessment of liver disease severity is recommended prior to therapy. Identifying patients with cirrhosis or advanced

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(bridging) fibrosis is of particular importance, as the post-treatment prognosis depends on the stage of fibrosis. The absence of significant fibrosis may also have important implications for stratification of disease and possibly the timing of therapy. Assessment of the stage of fibrosis is not required in patients with clinical evidence of cirrhosis. Patients with cirrhosis need surveillance for HCC. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT levels.

Liver biopsy has been for many years the reference method for grading the activity and histological progression (staging) of the disease. In chronic hepatitis C, considerable evidence suggest that non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictability. Liver stiffness measurement can be used to assess liver fibrosis in patients with chronic hepatitis C, provided that consideration is given to factors that may adversely affect its performance such as obesity. Well-established panels of biomarkers of fibrosis can also be applied. Both liver stiffness measurement and biomarkers perform well in the identification of cirrhosis or no fibrosis, but they perform less well in resolving intermediate degrees of fibrosis.

The combination of blood biomarkers or the combination of liver stiffness measurement and a blood test improve accuracy and reduce the need for liver biopsy to resolve uncertainty [20,21]. These tests are of particular interest in patients with coagulation disorders, though transjugular liver biopsy may also be used safely in this situation with the bonus that portal pressure can also be assessed. In case of contradictory results with non-invasive markers, liver biopsy may be indicated. Also, histology may be required in cases of known or suspected mixed aetiologies (e.g. HCV infection with HBV infection, metabolic syndrome, alcoholism or autoimmunity).

HCV RNA detection/quantification and genotype determination

HCV RNA detection/quantification is indicated for the patient who may undergo antiviral treatment. HCV RNA quantification should be made by a reliable sensitive assay, and HCV RNA levels should be expressed in IU/ml.

The HCV genotype, including genotype 1 subtype, should also be assessed prior to treatment initiation. Genotyping/subtyping should be performed with an assay that accurately discriminates subtype 1a from 1b [22].

HCV resistance testing prior to first-line therapy is not required. Indeed, the presence of pre-existing resistance-associated variants as detected by population sequencing does not have a major impact on the results of therapy and will not influence the treatment decision (with the exception of the effect of the Q80K substitution in patients with subtype 1a infection treated with the combination of PegIFN- α , ribavirin, and simeprevir, see below).

Determination of host genetics

IL28B genotyping has lost predictive value with the new highly efficacious IFN-free treatment regimens. Thus, *IL28B* genotyping is useful only in settings where only PegIFN- α and ribavirin are available or to select cost-effective treatment options in settings with economical restrictions.

Recommendations

- The causal relationship between HCV infection and liver disease should be established **(A1)**
- The contribution of comorbid conditions to the progression of liver disease must be evaluated and appropriate corrective measures implemented **(A1)**
- Liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted **(A1)**
- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional aetiologies **(A1)**
- HCV RNA detection and quantification should be made by a sensitive assay with a lower limit of detection of ≤ 15 IU/ml **(A1)**
- The HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy **(A1)**
- *IL28B* genotyping has no role in the indication for treating hepatitis C with the new DAAs **(A1)**
- HCV resistance testing should not be performed prior to therapy, because the SVR rates are very high both in patients without and with detectable amounts of resistance-associated variants by means of population sequencing at baseline (with the exception of patients infected with subtype 1a who receive the combination of PegIFN- α , ribavirin and simeprevir) **(A1)**

Contra-indications to therapy

IFN- α and ribavirin

Treatment of chronic hepatitis C with PegIFN- α and ribavirin-containing regimens is absolutely contra-indicated in the following patient groups: uncontrolled depression, psychosis or epilepsy; pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical diseases and comorbidities including retinal disease, autoimmune thyroid disease; decompensated liver disease.

The use of PegIFN- α is not recommended in patients with absolute neutrophil counts $<1500/\text{mm}^3$ and/or platelet counts $\leq 90,000/\text{mm}^3$. Treatment of patients with advanced liver disease whose parameters fall outside of label recommendations may be feasible in experienced centres under careful monitoring and informed consent.

Approved DAAs

Based on existing knowledge, no absolute contra-indications to the DAAs approved in the EU region in 2015 exist. Caution is

required with the use of sofosbuvir in patients with severe renal impairment, as the effect of impaired renal function on clearance of sofosbuvir-derived metabolites is still being ascertained. The combination of ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir is undergoing evaluation in patients with Child-Pugh B decompensated cirrhosis and is contra-indicated in patients with Child-Pugh C decompensated cirrhosis. Studies are on-going to assess the pharmacokinetics and safety of simeprevir in decompensated cirrhosis.

Indications for treatment: who should be treated?

All treatment-naïve and -experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contra-indications to treatment, should be considered for therapy. Because not every HCV-infected patient can be treated within the next year or so, prioritization is necessary (Table 2). The panel acknowledges that priorities may be modulated according to local and/or societal considerations.

Treatment priority should be based on fibrosis stage, risk of progression towards more advanced disease, presence of extra-hepatic manifestations of HCV infection and risk of HCV transmission. Treatment should be prioritized in patients with advanced fibrosis (METAVIR score F3 to F4), including patients with decompensated cirrhosis who have a contra-indication to the use of IFN- α but can be safely treated with IFN-free regimens. Indeed, data from clinical trials and real-life cohorts indicate that these patients could benefit more from a cure of HCV infection in the short-term, because substantial decreases in Child-Pugh and MELD scores and reductions in the incidence of clinical events have been observed. However, evidence for an improved outlook is still limited in patients with Child-Pugh scores above 12 and MELD scores higher than 20. IFN-free treatment in patients with decompensated disease should only be attempted in experienced centres until further safety and efficacy data have accumulated.

High priority groups also include patients with HIV or HBV coinfection, patients in the pre- or post-liver transplant setting, patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), and patients with debilitating fatigue, regardless of their liver fibrosis stage.

Treatment should also be prioritized regardless of the fibrosis stage or extra-hepatic manifestations in individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and incarcerated individuals. Injection drug users and men who have sex with men with high-risk sexual practices should be made aware of the risk of reinfection and should apply preventative measures after successful treatment.

Treatment is justified in patients with moderate fibrosis (METAVIR score F2). The timing and nature of therapy for patients with minimal or no fibrosis (METAVIR score F0–F1) and no severe extra-hepatic manifestations is debatable, and informed deferral can be considered. The decision to defer treatment for a specific patient should consider the patient's preference and priorities, the natural history and risk of progression, the presence of comorbidities, and the patient's age. Patients who have treatment deferred should be assessed on a regular

basis for evidence of progression, to reconsider the indication for treatment, and to discuss new therapies as they emerge or become available and affordable.

Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities.

Recommendations

- All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy **(A1)**
- Treatment should be prioritized for patients with significant fibrosis or cirrhosis (METAVIR score F3 to F4) **(A1)**
- Patients with decompensated cirrhosis (Child-Pugh B and C) should be urgently treated with an IFN-free regimen **(A1)**
- Treatment should be prioritized regardless of the fibrosis stage in patients with HIV or HBV coinfection, patients in the pre- or post-liver transplant setting, patients with clinically significant extra-hepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma), and patients with debilitating fatigue **(A1)**
- Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, haemodialysis patients, and incarcerated individuals **(B1)**
- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) **(A2)**
- In patients with no or mild disease (METAVIR score F0–F1) and none of the above-mentioned extra-hepatic manifestations, the indication for and timing of therapy can be individualized **(B1)**
- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities **(B1)**

Available drugs in the European Union in 2015

The HCV drugs available in the European Union are listed in this paragraph and in Table 3. Their known drug-drug interactions are also listed. For a more comprehensive listing of drug-drug interactions, see Tables 4A–F and www.hep-druginteractions.org.

PegIFN- α . PegIFN- α 2a should be used at the dose of 180 μ g/week, whereas PegIFN- α 2b should be used at the weight-based dose of 1.5 μ g/kg/week.

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Table 2. Indications for treatment of chronic hepatitis C in 2015: Who should be treated and when?

Treatment priority	Patient group
Treatment is indicated	<ul style="list-style-type: none"> All treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease
Treatment should be prioritized	<ul style="list-style-type: none"> Patients with significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis Patients with HIV coinfection Patients with HBV coinfection Patients with an indication for liver transplantation Patients with HCV recurrence after liver transplantation Patients with clinically significant extra-hepatic manifestations Patients with debilitating fatigue Individuals at risk of transmitting HCV (active injection drug users, men who have sex with men with high-risk sexual practices, women of child-bearing age who wish to get pregnant, haemodialysis patients, incarcerated individuals)
Treatment is justified	<ul style="list-style-type: none"> Patients with moderate fibrosis (F2)
Treatment can be deferred	<ul style="list-style-type: none"> Patients with no or mild disease (F0-F1) and none of the above-mentioned extra-hepatic manifestations
Treatment is not recommended	<ul style="list-style-type: none"> Patients with limited life expectancy due to non-liver related comorbidities

Table 3. Approved HCV drugs in the European Union in 2015.

Product	Presentation	Posology
PegIFN- α 2a	Solution for injection containing 180, 135 or 90 μ g of PegIFN- α 2a	Once weekly subcutaneous injection of 180 μ g (or less if dose reduction needed)
PegIFN- α 2b	Solution for injection containing 50 μ g per 0.5 ml of PegIFN- α 2b	Once weekly subcutaneous injection of 1.5 μ g/kg (or less if dose reduction needed)
Ribavirin	Capsules containing 200 mg of ribavirin	Two capsules in the morning and 3 in the evening if body weight <75 kg or Three capsules in the morning and 3 in the evening if body weight \geq 75 kg
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)

Ribavirin. The ribavirin dose should be 1000 or 1200 mg/day, based on body weight (<75 kg or \geq 75 kg, respectively).

Sofosbuvir should be administered at the dose of 400 mg (one tablet) once per day. Approximately 80% of sofosbuvir is renally excreted, whereas 15% is excreted in faeces. The majority of the sofosbuvir dose recovered in urine is the dephosphorylation-derived nucleoside metabolite GS-331007 (78%), while 3.5% is recovered as sofosbuvir. This indicates that renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. Currently, no sofosbuvir dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m²) or with end-stage renal disease due to higher exposures (up to 20-fold) of GS-331007. Sofosbuvir exposure is not significantly changed in patients with mild liver impairment, but it is increased 2.3-fold in those with moderate liver impairment.

Sofosbuvir is well tolerated over 12 to 24 weeks of administration. The most common adverse events (\geq 20%) observed in combination with ribavirin were fatigue and

headache. The most common adverse events (\geq 20%) observed in combination with PegIFN- α and ribavirin were fatigue, headache, nausea, insomnia and anaemia. Slight elevations of creatine kinase, amylase and lipase without clinical impact were also observed.

Sofosbuvir is not metabolised by cytochrome P450, but is transported by P-glycoprotein (P-gp). Drugs that are potent P-gp inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Thus sofosbuvir should not be administered with other known inducers of P-gp, such as rifampin, carbamazepine, phenytoin or St. John's wort. Other potential interactions may occur with rifabutin, rifampine, and modafinil. No other significant drug-drug interactions have been reported, in particular with all of the antiretroviral agents tested, including emtricitabine, tenofovir, rilpivirine, efavirenz, darunavir/ritonavir, and raltegravir, and there are no potential drug-drug interactions with the remaining antiretrovirals. Co-administration of amiodarone (and possibly dronedarone) with sofosbuvir in combination with daclatasvir, simeprevir or

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•	•
	Fosamprenavir	•	•	•	•	•
	Lopinavir	•	•	•	•	•
	Saquinavir	•	•	•	•	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

*Known or anticipated increase in tenofovir concentrations with boosted regimens and with efavirenz and rilpivirine when given sofosbuvir plus ledipasvir: caution and frequent renal monitoring needed.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

• 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.

ledipasvir is contra-indicated due to a serious risk of symptomatic bradycardia (one lethal case reported). The mechanism of interaction as well as the role of other co-medications is unknown and requires investigation. Bradycardia has been observed within hours to days of starting the DAAs, but cases have been observed up to 2 weeks after initiating HCV treatment.

Sofosbuvir and ledipasvir are available in a two-drug fixed-dose combination containing 400 mg of sofosbuvir and 90 mg of ledipasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food.

Biliary excretion of unchanged ledipasvir is the major route of elimination with renal excretion being a minor pathway (approximately 1%), whereas sofosbuvir is principally renally excreted, as noted above. The median terminal half-lives of sofosbuvir and its predominant metabolite GS-331007 following administration of sofosbuvir/ledipasvir were 0.5 and 27 h, respectively. Neither sofosbuvir nor ledipasvir are substrates for hepatic uptake transporters; GS-331007 is not a substrate for renal transporters.

Table 4B. Drug-drug interactions between HCV DAAs and illicit recreational drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hydroxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring.

• 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) 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.

Table 4C. Drug-drug interactions between HCV DAAs and lipid lowering drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

• 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.

Ledipasvir plasma exposure (AUC) was similar in patients with severe hepatic impairment and control patients with normal hepatic function. Population pharmacokinetics analysis in HCV-infected patients indicated that cirrhosis (including

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Table 4D. Drug-drug interactions between HCV DAAs and central nervous system drugs.

	SIM	DCV	SOF	SOF/LDV	3D
Anti-depressants	Amitriptyline	•	•	•	•
	Citalopram	•	•	•	•
	Duloxetine	•	•	•	•
	Escitalopram	•	•	•	•
	Fluoxetine	•	•	•	•
	Paroxetine	•	•	•	•
	Sertraline	•	•	•	•
	Trazodone	•	•	•	•
	Trimipramine	•	•	•	•
	Venlafaxine	•	•	•	•
Anti-psychotics	Amisulpiride	•	•	•	•
	Aripiprazole	•	•	•	•
	Chlorpromazine	•	•	•	•
	Clozapine	•	•	•	•
	Flupentixol	•	•	•	•
	Haloperidol	•	•	•	•
	Olanzapine	•	•	•	•
	Quetiapine	•	•	•	•
	Risperidone	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir. **Colour legend.** Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- 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.

decompensated cirrhosis) had no clinically relevant effect on the exposure to ledipasvir.

While no dose adjustment of sofosbuvir and ledipasvir is required for patients with mild or moderate renal impairment, the safety of the sofosbuvir-ledipasvir combination has not been assessed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m²) or end-stage renal disease requiring haemodialysis. Relative to patients with normal renal function (eGFR >80 ml/min/1.73 m²), 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. Thus, no dose adjustment is required for patients with mild or moderate renal impairment, but no dose recommendation can currently be given for patients with severe renal impairment (eGFR <30 ml/min/1.73 m²) or with end-stage renal disease.

The most common adverse reactions reported with this combination were fatigue and headache.

Since the combination contains ledipasvir and sofosbuvir, any interactions identified with the individual drugs will apply to the

Table 4E. Drug-drug interactions between HCV DAAs and cardiovascular drugs.

	SIM	DCV	SOF	SOF/LDV	3D
Antiarrhythmics	Amiodarone	•	•	•	•
	Digoxin	•	•	•	•
	Flecainide	•	•	•	•
	Vernakalant	•	•	•	•
Antiplatelet and anticoagulants	Clopidogrel	•	•	•	•
	Dabigatran	•	•	•	•
	Warfarin	•	•	•	•
Beta blockers	Atenolol	•	•	•	•
	Bisoprolol	•	•	•	•
	Propranolol	•	•	•	•
Calcium channel blockers	Amlodipine	•	•	•	•
	Diltiazem	•	•	•	•
	Nifedipine	•	•	•	•
Hypertension and heart failure agents	Aliskiren	•	•	•	•
	Candesartan	•	•	•	•
	Doxazosin	•	•	•	•
	Enalapril	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- 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.

combination. The potential (limited) interactions with sofosbuvir have been previously outlined. Since both ledipasvir and sofosbuvir are transported by P-gp and breast cancer resistant protein (BCRP), any co-administered drugs that are potent P-gp inducers will decrease not only sofosbuvir but also ledipasvir plasma concentrations, leading to reduced therapeutic effect. Although co-administration with drugs that inhibit P-gp and/or BCRP may increase the exposure of sofosbuvir and ledipasvir, clinical consequences are unlikely. One area of focus for ledipasvir interactions is the inhibition of P-gp and/or BCRP whereby ledipasvir may increase the intestinal absorption of co-administered drugs. Thus, caution is warranted with well-studied P-gp substrates such as digoxin and dabigatran, but also potentially with other drugs which are, in part, transported by these proteins (e.g. aliskiren, amlodipine, buprenorphine, carvedilol, cyclosporine). Co-administration of amiodarone (and possibly dronedarone) with sofosbuvir/ledipasvir is contra-indicated due to a serious risk of symptomatic bradycardia (see above, mechanism of interaction

Table 4F. Drug-drug interactions between HCV DAAs and immunosuppressants.

	SIM	DCV	SOF	SOF/LDV	3D
Azathioprine	•	•	•	•	•
Cyclosporine	•	•	•	•	•
Etanercept	•	•	•	•	•
Everolimus	•	•	•	•	•
Mycophenolate	•	•	•	•	•
Sirolimus	•	•	•	•	•
Tacrolimus	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- 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.

is unknown). The use of rosuvastatin is also not recommended (thought to be due to inhibition of OATP by ledipasvir) and interactions with other statins cannot be excluded. It is important to monitor carefully for statin adverse reactions. Since ledipasvir solubility decreases as pH increases, drugs that increase gastric pH (antacids, H₂-receptor antagonists, proton pump inhibitors) are likely to decrease concentrations of ledipasvir. H₂-receptor antagonists can be given simultaneously or 12 h apart at a dose not exceeding famotidine 40 mg and proton pump inhibitors simultaneously at a dose comparable to omeprazole 20 mg.

Ledipasvir/sofosbuvir may be given with all antiretrovirals. However, due to an increase in tenofovir concentrations when a pharmacokinetic enhancer (ritonavir or cobicistat) is present in an antiretroviral regimen, these combinations (i.e. atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir, elvitegravir/cobicistat, darunavir/cobicistat, all in combination with tenofovir/emtricitabine) should be used with caution, with frequent renal monitoring if other alternatives are not available. There are currently no safety and efficacy data of the combination of sofosbuvir and ledipasvir administered with boosted HIV protease-containing regimens and the interaction is not mitigated by staggering administration by 12 h. Tenofovir is also increased in efavirenz-containing regimens and caution is required.

Simeprevir should be administered at the dose of 150 mg (one capsule) once per day. Simeprevir is extensively bound to plasma proteins (>99.9%), primarily to albumin. Simeprevir primarily undergoes oxidative metabolism by the hepatic CYP3A system. Elimination occurs via biliary excretion, whereas renal excretion is negligible.

The mean steady-state AUC of simeprevir is 2.4-fold higher in HCV-uninfected subjects with moderate hepatic impairment (Child-Pugh B). It is 5.2-fold higher in HCV-uninfected subjects with severe hepatic impairment (Child-Pugh C). Simeprevir has not been extensively studied in such patients, but has been used

in real-life settings. However, substantially higher simeprevir exposures occur in this group and simeprevir is not recommended for these patients.

No dose adjustment of simeprevir is required in patients with mild, moderate or severe renal impairment. The safety and efficacy of simeprevir have not been studied in patients with a creatinine clearance below 30 ml/min or end-stage renal disease, including patients on dialysis. However, because simeprevir is highly protein-bound, dialysis is unlikely to result in significant removal of simeprevir.

Adverse reactions with at least 3% higher frequency in patients receiving simeprevir in combination with PegIFN- α and ribavirin were rash (including photosensitivity), pruritus and nausea. Because simeprevir is an inhibitor of the hepatic transporters OATP1B1 and MRP2 [23], mild, transient hyperbilirubinaemia not accompanied by changes in other liver parameters was observed in approximately 10% of cases.

Because the primary enzyme involved in the metabolism of simeprevir is CYP3A4, co-administration of simeprevir with substances that are moderate or strong inducers or inhibitors of CYP3A4 is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively. A number of compounds are contra-indicated in patients receiving simeprevir, including anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antibiotics (erythromycin, clarithromycin, telithromycin), antimycobacterials (rifampin, rifabutin, rifapentine), systemically administered antifungals (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole), systemically administered dexamethasone, cisapride, herbal products (milk thistle, St John's wort) and a number of antiretroviral drugs, including cobicistat-based regimens, efavirenz, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir. Raltegravir, maraviroc, rilpivirine, tenofovir, emtricitabine, lamivudine and abacavir have no interactions with simeprevir and can thus be safely used in patients receiving this drug. Dose adjustments are needed with some antiarrhythmics, warfarin, calcium channel blockers, HMG Co-A reductase inhibitors and sedative/anxiolytics.

No dose changes are required when used in combination with the immunosuppressants tacrolimus and sirolimus, although routine monitoring of blood concentrations of the immunosuppressant is recommended. In contrast, the use of simeprevir with cyclosporine resulted in significantly increased plasma concentrations of simeprevir (due to hepatic uptake transporter inhibition), such that it is not recommended to co-administer the drugs.

Daclatasvir should be administered at the dose of 60 mg (one tablet), or 30 mg (one tablet) when a reduced dose is needed, once per day. Approximately 90% of daclatasvir is eliminated in faeces (half as unchanged drug) and less than 10% is excreted in the urine (primarily as unchanged drug).

The pharmacokinetics of daclatasvir in non-HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment indicate that the exposure of total daclatasvir (free and protein-bound drug) is lower in subjects with hepatic impairment. However, hepatic impairment does not have a clinically significant effect on the free drug concentrations of daclatasvir. Thus, no dose adjustment of daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

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The pharmacokinetics of daclatasvir following a single 60 mg oral dose have been studied in non-HCV-infected subjects with renal impairment. Daclatasvir unbound AUC was estimated to be 18%, 39%, and 51% higher for subjects with creatinine clearance values of 60, 30, and 15 ml/min, respectively, relative to subjects with normal renal function. Subjects requiring haemodialysis had a 27% increase in daclatasvir AUC and a 20% increase in unbound AUC compared to subjects with normal renal function. Thus, no dose adjustment of daclatasvir is required for patients with any degree of renal impairment.

The most frequently reported side effects with daclatasvir were fatigue, headache and nausea.

Daclatasvir is a substrate of CYP3A4, and a substrate and inhibitor of P-gp. In addition, it is an inhibitor of OATP1B1 and BCRP. Co-administration of daclatasvir with drugs that strongly induce CYP3A4 and P-gp and thus reduce daclatasvir exposure is contra-indicated. This includes anticonvulsants (carbamazepine, phenytoin, oxcarbazepine, phenobarbital), antimycobacterials (rifampicin, rifabutin, rifapentine), systemic dexamethasone and St John's wort. Strong inhibitors of CYP3A4 increase the plasma levels of daclatasvir; therefore, dose adjustments of daclatasvir are recommended. The dose of daclatasvir should be reduced to 30 mg once daily with atazanavir/ritonavir and cobicistat containing antiretroviral regimens. In contrast, recent data suggest that no dose adjustment is necessary with either darunavir/ritonavir or lopinavir/ritonavir. In the ALLY-2 study in HIV-coinfected patients receiving sofosbuvir and daclatasvir, patients on a darunavir-based regimen who had daclatasvir dose reduced to 30 mg (based on the original atazanavir/ritonavir study data) had a reduced rate of SVR12, particularly in the 8-week treatment arm, pointing to the need for the standard dose of daclatasvir in patients on this boosted protease inhibitor. With efavirenz (an enzyme inducer), the dose of daclatasvir is recommended to be increased to 90 mg. Due to a lack of data, the same is not recommended with etravirine and nevirapine, both enzyme inducers. There are no drug interactions with tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, stavudine, rilpivirine, raltegravir, dolutegravir or maraviroc.

The dose of daclatasvir should also be reduced to 30 mg with the antibacterials clarithromycin, telithromycin, erythromycin and the antifungals ketoconazole, itraconazole, posaconazole and voriconazole. Studies have been performed with acid-reducing agents (famotidine, omeprazole), escitalopram and an oral contraceptive with no dose adjustment of daclatasvir or the co-medication. However, due to daclatasvir inhibiting some transport proteins, monitoring is required with dabigatran and digoxin and other P-gp substrates.

Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir.

Paritaprevir is an NS3-4A protease inhibitor which is metabolised primarily by CYP3A4 and is given with a low dose of the CYP3A inhibitor ritonavir as a pharmacokinetic enhancer. This enables once daily administration and a lower dose than would be required without ritonavir. Ombitasvir is an NSSA 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.

Pharmacokinetic results from hepatic impairment studies have shown that, in patients with severe hepatic impairment (Child-Pugh C), the AUC of paritaprevir was increased 9.5-fold, whereas ombitasvir was reduced 54% and dasabuvir was increased 3.3-fold. As a result, no dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A) and no dose adjustment is expected to be required for patients with moderate hepatic impairment (Child-Pugh B). In contrast, this combination is contra-indicated in patients with severe hepatic impairment (Child-Pugh C).

The AUC of paritaprevir was increased 45% in patients with severe renal impairment (creatinine clearance 15–29 ml/min), that of ritonavir 114%, and dasabuvir 50%. Currently, no dose adjustment is required for patients with mild, moderate or severe renal impairment. Whether paritaprevir, ombitasvir and/or dasabuvir are partly removed by dialysis is unknown.

The most common side effects reported with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir were fatigue and nausea.

Paritaprevir is primarily metabolised by CYP3A4, whereas dasabuvir is primarily metabolised by CYP2C8 and ombitasvir undergoes hydrolysis. However, both ombitasvir and dasabuvir can be metabolised by CYP3A4. Transporters seem to play an important role in the disposition of these drugs, with paritaprevir inhibiting OATP1B1/B3, P-gp and BCRP. Dasabuvir and ritonavir may also inhibit P-gp and BCRP. Given the metabolic profile of the drugs and the presence of ritonavir, there is a potential for many drug-drug interactions. A comprehensive drug-drug interaction programme has been undertaken based on regulatory guidance from both the European Medicines Agency and the US Food and Drug Administration. It is important to consider the drug interaction profile of the compounds as a combination (either with or without dasabuvir), because the drugs have mutual effects on each other.

Ritonavir is a strong inhibitor of CYP3A4; thus, co-administration with drugs metabolised by this enzyme may result in markedly increased plasma concentrations. A number of drugs are contra-indicated because elevated plasma exposure would lead to serious adverse events, including: alfuzosin, amiodarone, astemizole, terfenadine, cisapride, ergot derivatives, lovastatin, simvastatin, atorvastatin, oral midazolam, triazolam, quetiapine, quinidine, salmeterol, sildenafil when used for pulmonary arterial hypertension. Also contra-indicated are enzyme inducers that might compromise virological efficacy, e.g. carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort, enzalutamide, and enzyme inhibitors that might increase paritaprevir exposure, e.g. azole antifungals, some macrolide antibiotics.

In addition to the contra-indications, there are other drugs where caution needs to be exercised and there may be requirement for a dosage adjustment, altered timing of administration or additional monitoring. Drug interactions need to be carefully considered in the setting of coinfection with HIV. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contra-indicated. Efavirenz, etravirine and nevirapine are contra-indicated, and rilpivirine should be used cautiously with repeat ECG monitoring. The exposure of raltegravir and dolutegravir may be increased, but this is not linked to

safety issues. Elvitegravir/cobicistat should not be used because of the additional boosting effect.

Recommendations

- Numerous and complex drug-drug interactions are possible with the HCV DAAs, especially when they are used in IFN-free combinations. Strict rules should thus be applied. As the data accumulate, guidance for contra-indications and dose adjustments can be found in Tables 4A to 4F of these Recommendations and at www.hep-druginteractions.org where they are regularly updated (B1)
- The use of cobicistat-based regimens, efavirenz, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir (A1)
- The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz (B2)
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (A2)
- The fixed-dose combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/cobicistat when possible, or used with caution with frequent renal monitoring (B1)
- The combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should not be used with efavirenz, etravirine or nevirapine, and rilpivirine should be used cautiously with repeat ECG monitoring. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contra-indicated with this combination. Elvitegravir/cobicistat should not be used with this regimen because of the additional boosting effect (B1)

Treatment of chronic hepatitis C, including patients without cirrhosis and patients with compensated (Child-Pugh A) cirrhosis

In 2015 and onwards, treatment-naïve and treatment-experienced patients with compensated and decompensated liver disease will benefit from a broad choice of drug combinations. Indications will depend on the HCV genotype/subtype, the severity of liver disease, and/or the results of prior therapy. Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available, because of their virological efficacy, ease of use and tolerability. The indications are the same in HCV-monoinfected and HIV-coinfected patients. However, treatment alterations or dose adjustments may be needed in the latter due to drug-drug interactions (see above, drug-drug interactions).

Recommendations

- Indications for HCV treatment in HCV/HIV coinfecting persons are identical to those in patients with HCV-monoinfection (A1)
- Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available in HCV-monoinfected and in HIV-coinfected patients without cirrhosis or with compensated (Child-Pugh A) or decompensated (Child-Pugh B or C) cirrhosis, because of their virological efficacy, ease of use and tolerability (A1)
- The same IFN-free treatment regimens can be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical (A1)

For each genotype, the available options are described below, followed by a summary of the data available for the given option, and summarized in Tables 5 and 6.

Treatment of HCV genotype 1 infection

Six treatment options are available in 2015 for patients infected with HCV genotype 1, including two IFN-containing regimens and four IFN-free regimens. The combination of sofosbuvir and ribavirin should not be used in patients infected with HCV genotype 1. In settings where none of the proposed options is available, the double combination of PegIFN- α and ribavirin, or the triple combination of PegIFN- α , ribavirin and either telaprevir or boceprevir, remain acceptable for selected patients likely to respond to these regimens until new DAAs become available and affordable; see prior EASL Clinical Practice Guidelines [5,24].

IFN-containing options

Genotype 1, IFN-containing Option 1

- Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (A1)

Comments: This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients [25]. The overall SVR rate was 89% (259/291), 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b. Patients with cirrhosis had a lower SVR rate than non-cirrhotic patients (80% vs. 92%, respectively). Patients who failed on this regimen did not select HCV variants resistant to sofosbuvir. No Phase II data with this regimen has been presented in patients who failed prior PegIFN- α and ribavirin treatment. However, based on SVR rates in historical studies and the NEUTRINO trial, the US Food and Drug Administration predicted that 78% of patients who failed prior PegIFN- α and ribavirin treatment would achieve an SVR with the triple combination of PegIFN- α , ribavirin and sofosbuvir (although different models yielded slightly different predictions) [26]. Similarly, there is no data with this regimen in patients who failed prior PegIFN- α ,

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ribavirin and either telaprevir or boceprevir treatment. The SVR12 rate with the triple combination of PegIFN- α , ribavirin and sofosbuvir was 74% in patients who failed to achieve an SVR after receiving PegIFN- α , ribavirin and an investigational protease inhibitor alone or in combination with a non-nucleoside inhibitor of the HCV RNA-dependent RNA polymerase or ledipasvir [27]. There is no data with this combination in HIV-coinfected patients, and relatively small numbers of patients with cirrhosis were included. Whether longer treatment duration would be needed in the most difficult-to-cure population is unknown.

Preliminary results from two large-scale US real-life studies have been presented. In HCV TARGET 2.0 [13], the overall SVR4 rate with the triple combination of PegIFN- α , ribavirin and sofosbuvir was 85% (140/164; 55% were treatment-naïve and 45% treatment-experienced patients). SVR4 was achieved in 90% (114/127) of non-cirrhotic patients but 70% (26/37) of cirrhotic patients. In the TRIO real-life study, which included 58% of treatment-naïve and 42% of treatment-experienced patients, SVR12 was achieved in 81% (112/138) of treatment-naïve non-cirrhotic patients and 81% (25/31) of treatment-naïve cirrhotic patients, and in 77% (30/39) of treatment-experienced patients without cirrhosis and 62% (53/85) of treatment-experienced patients with cirrhosis (intent-to-treat) receiving PegIFN- α , ribavirin and sofosbuvir [28].

Genotype 1, IFN-containing Option 2

- Patients infected with HCV genotype 1 can be treated with a combination of weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily simeprevir (150 mg) (**A1**)
- This combination is not recommended in patients infected with subtype 1a who have a detectable Q80K substitution in the NS3 protease sequence at baseline, as assessed by population sequencing (direct sequence analysis) (**A1**)
- Simeprevir should be administered for 12 weeks in combination with PegIFN- α and ribavirin. PegIFN- α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotic patients, and for an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients (**B1**)
- HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is \geq 25 IU/ml at treatment week 4, week 12 or week 24 (**A2**)

Comments: This combination has been evaluated in the QUEST-1 and QUEST-2 Phase III clinical trials in treatment-naïve patients [29,30]. The overall SVR rates were 80% (210/264) and 81% (209/257), respectively. In a pooled analysis of both trials, patients infected with subtype 1b achieved an SVR in 85% of cases (228/267). Patients infected with subtype 1a achieved an SVR in 84% of cases (138/165) when no Q80K substitution was detectable in the NS3 protease sequence at baseline. The SVR was only 58% (49/84) when a Q80K substitution was detectable at baseline by population sequencing. SVR was achieved with this regimen in 84% (317/378) of patients with an F0-F2 METAVIR score, 73% (60/

82) of patients with F3, and 60% (29/48) of patients with F4 (cirrhosis). However, for patients who received 24 weeks of treatment, the SVR rate was lower in those with detectable than in those with undetectable HCV RNA at treatment week 4 (69% vs. 93%, respectively) [29,30]. In treatment-naïve, HIV-coinfected patients receiving this treatment regimen, SVR was achieved in 79% of patients (42/53) [31].

In monoinfected patients who previously relapsed to IFN- α /ribavirin-based therapy, SVR24 was achieved in 86% (128/149) of subtype 1b patients and in 70% (78/111) of subtype 1a patients. Among patients infected with genotype 1a, SVR24 was achieved in 78% of those without and 47% of those with a detectable Q80K substitution at baseline [32]. The SVR rate in HIV-coinfected relapsers was 87% (13/15) in another study [31].

In the ATTAIN Phase III study, SVR12 was achieved in 70% (101/145) of prior partial responders and 44% (102/234) of null responders to IFN- α /ribavirin-based therapy treated with the triple combination of PegIFN- α , ribavirin and simeprevir, vs. 68% (100/146) and 46% (110/238) of the same groups who received telaprevir, respectively [33]. In HIV-coinfected patients, 70% (7/10) of partial responders and 54% (15/28) of null responders achieved an SVR24 in another study [31].

IFN-free options

Genotype 1, IFN-free Option 1

- Patients infected with HCV genotype 1 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**)
- Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin (**A1**)
- Treatment may be shortened to 8 weeks in treatment-naïve patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 Log) IU/ml. This should be done with caution, especially in patients with F3 fibrosis, pending demonstration of the accuracy of HCV RNA level determination within this range of values and real-life confirmation that 8 weeks of treatment are sufficient to achieve high SVR rates (**B1**)
- Patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) (**A1**)
- Patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin (**B1**)
- Treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 $\times 10^3/\mu\text{l}$ (**B2**)

Table 5. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfecting patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN- α and ribavirin (RBV).

Patients	PegIFN- α , RBV and sofosbuvir	PegIFN- α , RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN- α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN- α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfecting patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on PegIFN- α and ribavirin (RBV).

Patients	PegIFN- α , RBV and sofosbuvir	PegIFN- α , RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treatment-naïve or relapsers) or 24 wk (partial or null responders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

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Comments: This recommendation is based on the results of the three Phase III trials ION-1, ION-2 and ION-3 [34–36]. In ION-1, treatment-naïve patients, including 16% with compensated cirrhosis, achieved SVR12 in 99% (211/214) and 97% (211/217) of cases after 12 weeks of the fixed-dose combination of sofosbuvir and ledipasvir without or with ribavirin, respectively. The SVR12 rates were 98% (212/217) and 99% (215/217) after 24 weeks of the same combination without or with ribavirin, respectively [34]. In ION-3 in treatment-naïve patients without cirrhosis (F3 in only 13% of patients who underwent liver biopsy), the SVR12 rates were 94% (202/215) without ribavirin for 8 weeks, 93% (201/216) with ribavirin for 8 weeks and 95% (205/216) without ribavirin for 12 weeks. The absolute number of post-treatment relapses was, however, higher in the 8-weeks arms: 11/215, 9/216 and 3/216, respectively. Post hoc analysis indicated that only patients with an HCV RNA level <6 million (6.8 Log) IU/ml at baseline could be treated for 8 weeks [36]. However, HCV RNA level determination can be inaccurate within this range of values with currently available HCV RNA assays and real-life confirmation is needed to determine that 8 weeks of treatment with this combination is sufficient. Interestingly, the relapse rates were 1% (1/84) and 1% (1/96) in female patients treated for 8 weeks with sofosbuvir and ledipasvir without and with ribavirin, respectively, and 8% (10/129) and 7% (8/114) in males, respectively, in the ION-3 study [36]. In another Phase II study, the combination of sofosbuvir and ledipasvir was given for 12 weeks without ribavirin to patients with HCV genotype 1 infection coinfecting with HIV, including 13 not treated for their HIV infection and 37 receiving antiretroviral therapy. All but one patient (98%) achieved an SVR12 [37].

In ION-2, in treatment-experienced patients (prior PegIFN- α and ribavirin or PegIFN- α , ribavirin and either telaprevir or boceprevir), including 20% with cirrhosis, the SVR12 rates were 94% (102/109) and 96% (107/111) without or with ribavirin, respectively. After 24 weeks of therapy, SVR rates were 99% (108/109) and 99% (110/111), respectively [37].

An integrated analysis of 513 genotype 1 patients with compensated cirrhosis treated with the fixed-dose combination of sofosbuvir and ledipasvir, with or without ribavirin, in different Phase II and III studies showed overall SVR12 rates of 95% (305/322) after 12 weeks and 98% (188/191) after 24 weeks of therapy [38]. Neither treatment duration nor ribavirin had an impact on SVR12 in treatment-naïve patients (SVR12 rates between 96% and 100%). In contrast, in treatment-experienced patients, the SVR12 rates were 90% after 12 weeks without ribavirin, 96% after 12 weeks with ribavirin, 98% after 24 weeks without ribavirin, and 100% after 24 weeks with ribavirin. A platelet count $<75 \times 10^3/\mu\text{l}$ was associated with a lower rate of SVR among treatment-experienced patients (based on 28 patients) [38].

In the SIRIUS study, 12 weeks of the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin or 24 weeks of the same combination without ribavirin in patients with compensated cirrhosis who failed to achieve an SVR after treatment with PegIFN- α , ribavirin and either telaprevir or boceprevir yielded SVR12 rates of 96% (74/77) and 97% (75/77), respectively [39].

Genotype 1, IFN-free Option 2

- Patients infected with HCV genotype 1 can be treated with an IFN-free regimen comprising the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), and dasabuvir (250 mg) (one tablet twice daily) (A1)
- Patients infected with subtype 1b without cirrhosis should receive this combination for 12 weeks without ribavirin (A1)
- Patients infected with subtype 1b with cirrhosis should receive this combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively) (A1)
- Patients infected with subtype 1a without cirrhosis should receive this combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively) (A1)
- Patients infected with subtype 1a with cirrhosis should receive this combination for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively) (A1)

Comments: This recommendation is based on the results of seven Phase III trials. In SAPPPIRE-I in treatment-naïve patients without cirrhosis treated with this combination together with ribavirin for 12 weeks, the SVR12 rates were 95% (307/322) in subtype 1a and 98% (148/151) in subtype 1b patients [40]. In PEARL-IV, the SVR12 rates were 90% (185/205) and 97% (97/100) without and with ribavirin, respectively, in treatment-naïve non-cirrhotic patients infected with subtype 1a. In PEARL-III, the SVR12 rates were 99% (207/209) and 99% (209/210) without and with ribavirin, respectively, in treatment-naïve non-cirrhotic patients infected with subtype 1b [41]. In the TURQUOISE-I study in treatment-naïve, non-cirrhotic patients coinfecting with HIV-1 and stable on antiretroviral treatment containing atazanavir or raltegravir, the SVR12 rates were 93% (29/31) and 91% (29/32) after 12 or 24 weeks of treatment, respectively; SVR12 was achieved in 91% (51/56) of subtype 1a and 100% (7/7) of subtype 1b patients [42].

In non-cirrhotic treatment-experienced patients (PegIFN- α and ribavirin failures) treated with this combination with ribavirin for 12 weeks in SAPPPIRE-II, the SVR12 rates were 96% (166/173) in subtype 1a and 97% (119/123) in subtype 1b patients. Overall, the SVR12 rates were 95% (82/86) in prior relapsers, 100% (65/65) in prior partial responders and 95% (139/146) in prior null responders [43]. SVR12 was achieved in 100% (91/91) of cases without ribavirin and 97% (85/88) with ribavirin in patients infected with subtype 1b receiving this combination in the PEARL-II trial [44].

In treatment-naïve and treatment-experienced patients with compensated cirrhosis, the rates of SVR were 92% (191/208) after 12 weeks and 96% (165/172) after 24 weeks of the combination

of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir plus ribavirin in the TURQUOISE-II trial. SVR12 was achieved in 92% (239/261) of genotype 1a and 99% (118/119) of genotype 1b patients [45]. In patients with α -fetoprotein level <20 ng/ml, platelet count $\geq 90 \times 10^9/L$ and albumin level ≥ 35 g/L prior to treatment, the relapse rates were 1% (1/87) and 0% (0/68) after 12 or 24 weeks of treatment, respectively; in patients with α -fetoprotein level ≥ 20 ng/ml and/or platelet count $<90 \times 10^9/L$ and/or albumin level <35 g/L prior to treatment, they were 21% (10/48) and 2% (1/45) after 12 or 24 weeks of treatment, respectively [45].

Genotype 1, IFN-free Option 3

- Patients infected with HCV genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks (**A1**)
- Based on data with other IFN-free combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively) is recommended in patients with cirrhosis (**B1**)
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B1**)

Comments: This recommendation is based on results from the COSMOS Phase IIb trial [11]. In the first cohort, 80 prior null responders to PegIFN- α and ribavirin therapy with a METAVIR score F0 to F2 were treated 12 or 24 weeks, with or without ribavirin. The SVR12 rates were 93% (13/14) and 96% (26/27) for 12 weeks of therapy without and with ribavirin, respectively, and 93% (14/15) and 79% (19/24) for 24 weeks of therapy without and with ribavirin, respectively. In the second cohort, 87 treatment-naïve patients and prior null responders with a METAVIR score of F3–F4 were treated 12 or 24 weeks, without or with ribavirin. The SVR12 rates were 93% (13/14) and 93% (25/27) for 12 weeks of therapy without and with ribavirin, respectively, and 100% (16/16) and 93% (28/30) for 24 weeks of therapy without and with ribavirin, respectively. All virological failures were due to post-treatment relapses [11].

Preliminary results from two large-scale US real-life studies with sofosbuvir and simeprevir indicate that this combination is well tolerated and yields high SVR rates, which are however lower than those reported in the COSMOS trial, in particular in patients with advanced stages of liver disease [13,28]. These studies are not conclusive as to the value of adding ribavirin to the sofosbuvir-simeprevir combination (ribavirin addition was at the prescriber's discretion and may have been influenced by various pretreatment parameters). In HCV TARGET 2.0 [13], the overall SVR4 rate was 89% (269/303). SVR4 was achieved in 92% (113/123) of non-cirrhotic patients, 87% (156/180) of cirrhotic patients, and 75% (61/81) of cirrhotic patients with prior decompensation. SVR4 was more frequent in subtype 1b than 1a patients: 95% (88/93) and 89% (47/53), respectively. SVR4 was achieved in 81% (44/54) of patients who failed on a prior treatment with PegIFN- α , ribavirin and either telaprevir or boceprevir, including in 85% (17/20) of non-cirrhotic patients and 79% (27/34) of cirrhotic patients. Preliminary data from the TRIO real-life study showed

SVR12 in 88% (68/88) of treatment-naïve non-cirrhotic and 75% (41/55) of treatment-naïve cirrhotic patients; SVR rates were 87% (64/74) and 76% (53/70) in treatment-experienced non-cirrhotic and cirrhotic patients, respectively (intent-to-treat) [28].

Genotype 1, IFN-free Option 4

- Patients infected with HCV genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks (**A1**)
- Based on data with other IFN-free combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively) is recommended in patients with cirrhosis (**B1**)
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B1**)

Comments: Phase IIb results have been published with this combination in patients without cirrhosis [14]. With 24 weeks of therapy, the SVR rates were 100% (14/14 and 15/15, without and with ribavirin, respectively) in treatment-naïve patients, and 100% (21/21) and 95% (19/21) without and with ribavirin, respectively, in patients who did not respond to the combination of PegIFN- α , ribavirin, and either telaprevir or boceprevir. With 12 weeks of therapy, SVR was achieved in 98% (40/41) of treatment-naïve patients without ribavirin (the remaining patient was lost to follow-up) [14]. Large-scale real-life data from European early access programmes will be presented in 2015.

Treatment of HCV genotype 2 infection

The best first-line treatment option for patients infected with HCV genotype 2 is the IFN-free combination of sofosbuvir and ribavirin. Other options may be useful in the small number of patients who fail on this regimen. In settings where these options are not available, the combination of PegIFN- α and ribavirin remains acceptable, according to previously published EASL Clinical Practice Guidelines [5].

Genotype 2, Option 1

- Patients infected with HCV genotype 2 must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥ 75 kg, respectively), and daily sofosbuvir (400 mg) for 12 weeks (**A1**)
- Therapy should be prolonged to 16 or 20 weeks in patients with cirrhosis, especially if they are treatment-experienced (**B1**)

Comments: Results from four Phase III trials have been published. In the FISSION trial in treatment-naïve patients treated 12 weeks [25], the SVR rate was 95% (69/73). The response rate was better in patients without cirrhosis (97% vs. 83% in patients

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without and with cirrhosis, respectively). The POSITRON trial included patients considered ineligible or intolerant to IFN, who were treated for 12 weeks with sofosbuvir and ribavirin [46]. SVR was achieved in 93% (101/109) of cases. When comparing 12 and 16 weeks of therapy in the FUSION trial [46], SVR was achieved in 82% (32/39) and 89% (31/35) of cases, respectively, 60% (6/10) and 78% (7/9) in patients with cirrhosis, respectively. This indicates that patients with cirrhosis may benefit from longer than 12 weeks of therapy. In the VALENCE trial [47], the SVR rates after 12 weeks of treatment were 97% (29/30) in treatment-naïve non-cirrhotic individuals, 100% (2/2) in treatment-naïve cirrhotic patients, 91% (30/33) in treatment-experienced non-cirrhotic patients, and 88% (7/8) in treatment-experienced cirrhotic patients. In another study, 1 of 2 patients who relapsed after treatment with sofosbuvir and ribavirin retreated 24 weeks with sofosbuvir and ribavirin achieved an SVR [48]. The combination of sofosbuvir and ribavirin was well tolerated in all these studies. No virological breakthroughs were observed in treatment-adherent patients, and relapses were not associated with the selection of resistant HCV variants.

Genotype 2, Option 2

- Cirrhotic and/or treatment-experienced patients can be treated with weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**B1**)

Comments: In the LONESTAR-2 Phase IIb study [49], a single centre study in which 23 treatment-experienced patients infected with HCV genotype 2, including 14 with cirrhosis, received 12 weeks of PegIFN- α , ribavirin and sofosbuvir, the SVR rate was 96%. In another study, 4/4 patients who relapsed after treatment with sofosbuvir and ribavirin retreated 12 weeks with the triple combination of PegIFN- α , ribavirin and sofosbuvir achieved an SVR [48].

Genotype 2, Option 3

- Cirrhotic and/or treatment-experienced patients can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks (**B1**)

Comments: Daclatasvir is active against genotype 2 *in vitro*. In a Phase II trial, 92% (24/26) of patients infected with genotype 2 achieved an SVR12 after 24 weeks of sofosbuvir and daclatasvir. Based on data with other, more difficult-to-cure HCV genotypes, 12 weeks is probably sufficient for this regimen that should be reserved for patients who failed with other options.

Treatment of HCV genotype 3 infection

Three treatment options are available for patients infected with HCV genotype 3. The combination of sofosbuvir and ribavirin is suboptimal, in particular in patients with cirrhosis who have previously failed IFN and ribavirin. Based on data with other

genotypes and results in a small group of genotype 3-infected patients, the triple combination of PegIFN- α , ribavirin and sofosbuvir appears to be valuable. The IFN-free combination of sofosbuvir and daclatasvir, with or without ribavirin, is another attractive option for patients infected with HCV genotype 3.

Ledipasvir is considerably less potent against genotype 3 than daclatasvir *in vitro*; in clinical trials with ledipasvir, the respective roles of ledipasvir and ribavirin in combination with sofosbuvir cannot be determined in the absence of control arms with sofosbuvir and ribavirin alone. Thus, although this combination has been used, pending further studies in larger populations including appropriate control arms, the combination of sofosbuvir plus ledipasvir is not recommended in patients infected with HCV genotype 3.

In settings where none of these options is available, the combination of PegIFN- α and ribavirin remains acceptable, according to previous EASL Clinical Practice Guidelines [5].

Genotype 3, Option 1

- Patients infected with HCV genotype 3 can be treated with a combination of weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**B1**)
- This combination is a valuable option in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment (**B1**)

Comments: This combination has been evaluated in 10 treatment-naïve non-cirrhotic patients infected with genotype 3. Nine of them achieved an SVR, whereas the remaining one was lost to follow-up [50]. In addition, data with this combination in patients infected with HCV genotype 3 are available from the LONESTAR-2 Phase IIb trial in treatment-experienced individuals [49], who achieved an SVR in 83% (20/24) of cases, including 10/12 patients with cirrhosis. However, the pangenotypic activity of sofosbuvir together with high SVR rates with other genotypes (89% (259/291) overall for genotypes 1 and 4 to 6) indicate that this combination can be safely used in patients infected with HCV genotype 3. In another study, patients infected with genotype 3 who relapsed after treatment with sofosbuvir and ribavirin retreated with the triple combination of PegIFN- α , ribavirin and sofosbuvir for 12 weeks achieved an SVR in 91% (20/22) of cases [48].

Genotype 3, Option 2

- Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) for 24 weeks (**A1**)
- This therapy is suboptimal in treatment-experienced cirrhotic patients and in patients who failed to achieve an SVR after sofosbuvir plus ribavirin treatment, who should be offered an alternative treatment option (**B1**)

Comments: Results from four Phase III trials have been published. In the FISSION trial in treatment-naïve patients treated 12 weeks [25], the SVR rate was 56% (102/183). The response rate was better in patients without cirrhosis (61% and 34% in patients without and with cirrhosis, respectively). The POSITRON trial included patients ineligible or intolerant to IFN-based therapy who were treated for 12 weeks with sofosbuvir and ribavirin [46]; SVR was achieved in 61% (60/98) of cases. When comparing 12 and 16 weeks of therapy in the FUSION trial [46], SVR was achieved in 30% (19/64) and 62% (39/63) of cases, respectively, 19% (5/26) and 61% (14/23) in patients with cirrhosis, respectively. In the VALENCE trial [51], the SVR rates after 24 weeks of treatment were 94% (86/92) in treatment-naïve non-cirrhotic individuals, 92% (12/13) in treatment-naïve cirrhotics, 87% (87/100) in treatment-experienced non-cirrhotic patients, and 60% (27/45) in treatment-experienced cirrhotic patients. These results indicate that 24 weeks is the appropriate duration for this regimen in patients infected with HCV genotype 3, and that this regimen is suboptimal in treatment-experienced patients with cirrhosis. In another study, patients infected with genotype 3 who relapsed after treatment with sofosbuvir and ribavirin and were retreated 24 weeks with sofosbuvir and ribavirin achieved an SVR in only 63% (24/38) of cases, indicating that this regimen is suboptimal in such patients [48].

The combination of sofosbuvir and ribavirin was well tolerated and very few patients stopped therapy. No virological breakthroughs were observed in treatment-adherent patients, and relapses were not associated with the selection of resistant HCV variants.

Genotype 3, Option 3

- Patients infected with HCV genotype 3 without cirrhosis can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks (**A1**)
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should receive this combination with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 24 weeks, pending further data comparing 12 weeks with ribavirin and 24 weeks with and without ribavirin in this population (**B1**)

Comments: In a Phase IIb trial with this combination for 24 weeks [14], the SVR rate was 89% (16/18) in treatment-naïve non-cirrhotic patients infected with HCV genotype 3. In the ALLY-3 Phase III trial, patients were treated for 12 weeks with the combination of sofosbuvir and daclatasvir, without ribavirin. The SVR12 rates were 97% (73/75) and 58% (11/19) in treatment-naïve non-cirrhotic and cirrhotic patients, respectively; they were 94% (32/34) and 69% (9/13) in treatment-experienced non-cirrhotic and cirrhotic patients, respectively [52]. This regimen was well tolerated, with rare adverse events, none of which led to treatment discontinuation. The impact of pre-existing substitutions in the NS5A protein sequence known to confer resistance to daclatasvir at baseline on the response is unknown with this genotype.

Treatment of HCV genotype 4 infection

Six treatment options are available in 2015 for patients infected with HCV genotype 4, including two IFN-containing regimens and four IFN-free regimens. In settings where none of these options is available, the combination of PegIFN- α and ribavirin remains acceptable; see prior EASL Clinical Practice Guidelines [5].

IFN-containing options

Genotype 4, IFN-containing Option 1

- Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**B1**)

Comments: This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients [25]. The SVR rate in genotype 4 patients was 96% (27/28). The patient who failed on this regimen did not select HCV variants resistant to sofosbuvir. No data with this regimen is available in treatment-experienced patients or in HIV-coinfected patients. Whether longer treatment duration would be needed in the most difficult-to-treat population is unknown.

Genotype 4, IFN-containing Option 2

- Patients infected with HCV genotype 4 can be treated with a combination of weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily simeprevir (150 mg) (**B1**)
- Simeprevir should be administered 12 weeks in combination with PegIFN- α and ribavirin. PegIFN- α and ribavirin should then be administered alone for an additional 12 weeks (total treatment duration 24 weeks) in treatment-naïve and prior relapser patients, including cirrhotic patients, an additional 36 weeks (total treatment duration 48 weeks) in prior partial and null responders, including cirrhotic patients (**B1**)
- HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/ml at treatment week 4, week 12 or week 24 (**A2**)

Comments: Simeprevir is active against genotype 4 *in vitro*. Phase III data in 107 patients infected with genotype 4 indicate that the combination of PegIFN- α , ribavirin and simeprevir is effective in treatment-naïve patients and prior relapsers to IFN-based treatment, but suboptimal in prior partial responders and null responders [53]. Indeed, SVR12 was achieved in 83% (29/35) of treatment-naïve patients, 86% (19/22) of prior relapsers, 60% (6/10) of prior partial responders, and 40% (16/40) of prior null responders. No patient had a Q80K substitution detectable in the NS3 protease sequence at baseline.

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IFN-free options

Genotype 4, IFN-free Option 1

- Patients infected with HCV genotype 4 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**)
- Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin (**A1**)
- Based on data in patients infected with HCV genotype 1, patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**)
- Patients with compensated cirrhosis with contra-indications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin (**B1**)
- Based on data in patients infected with HCV genotype 1, treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 × 10³/μl (**B1**)

Comments: The SYNERGY trial assessed the efficacy and safety of the combination of sofosbuvir and ledipasvir without ribavirin in patients with genotype 4 infection. After 12 weeks of therapy, 95% (20/21) of them achieved an SVR (the remaining patient withdrew consent at week 4) [54]. It is unclear whether treatment duration can be shortened to 8 weeks (as in certain patients infected with genotype 1 based on the ION-3 study results) because of the lack of data with genotype 4.

Genotype 4, IFN-free Option 2

- Patients infected with HCV genotype 4 without cirrhosis can be treated with an IFN-free regimen comprising the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without dasabuvir (**A1**)
- Patients infected with HCV genotype 4 with cirrhosis should be treated with the fixed-dose combination of ombitasvir (12.5 mg), paritaprevir (75 mg) and ritonavir (50 mg) in one single tablet (two tablets once daily with food), for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without dasabuvir, pending further data (**B1**)

Comments: This recommendation is based on the results of the PEARL-I trial, in which treatment-naïve and treatment-experienced patients infected with genotype 4 treated for 12 weeks with ritonavir-boosted paritaprevir and ombitasvir (without dasabuvir) with ribavirin achieved SVR12 in 100% (42/42) and 100% (49/49) of cases, respectively [55]. Importantly, this study included only non-cirrhotic patients. An on-going study will conclude as to the duration of treatment needed with this regimen for patients infected with genotype 4 with cirrhosis.

Genotype 4, IFN-free Option 3

- Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks (**B2**)
- Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis (**B2**)
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B2**)

Comments: There is no data with this combination in patients infected with HCV genotype 4. Nevertheless, given the antiviral effectiveness of both sofosbuvir and simeprevir against this genotype, it is likely that the results of the COSMOS trial in patients infected with genotype 1 can be extrapolated [11].

Genotype 4, IFN-free Option 4

- Patients infected with HCV genotype 4 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks (**B2**)
- Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in patients with cirrhosis (**B2**)
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B2**)

Comments: There is no data with this combination in patients infected with HCV genotype 4. Nevertheless, given the antiviral effectiveness of both sofosbuvir and daclatasvir against this genotype *in vitro*, it is likely that the results in patients infected with genotype 1 can be extrapolated.

Treatment of HCV genotype 5 or 6 infection

The three treatment options for patients infected with HCV genotypes 5 or 6 are the triple combination of PegIFN-α, ribavirin and sofosbuvir, the IFN-free combination of sofosbuvir and ledipasvir, and the IFN-free combination of sofosbuvir and

daclatasvir. In settings where none of these options is available, the combination of PegIFN- α and ribavirin remains acceptable [5].

Genotype 5 or 6, Option 1

- Patients infected with HCV genotype 5 or 6 can be treated with a combination of weekly PegIFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks **(B1)**

Comments: This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients [25]. The single patient with genotype 5 and all 6 patients with genotype 6 achieved an SVR. No data with this regimen has been presented in treatment-experienced patients. Whether longer treatment duration would be needed in the most difficult-to-treat population is unknown.

Genotype 5 or 6, Option 2

- Patients infected with HCV genotype 5 or 6 can be treated with the IFN-free fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily **(A1)**
- Patients without cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks without ribavirin **(B1)**
- Based on data in patients infected with HCV genotype 1, patients with compensated cirrhosis, including treatment-naïve and treatment-experienced patients, should be treated with this fixed-dose combination for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) **(B1)**
- Patients with compensated cirrhosis with contra-indications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir for 24 weeks without ribavirin **(B1)**
- Based on data in patients infected with HCV genotype 1, treatment with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin can be prolonged to 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75 $\times 10^3/\mu\text{l}$ **(B1)**

Comments: Ledipasvir is active against both genotype 5 and 6 *in vitro*. No data is available with this combination for genotype 5. The combination of sofosbuvir and ledipasvir, administered 12 weeks without ribavirin in treatment-naïve and treatment-experienced patients infected with genotype 6 yielded an SVR rate of 96% (24/25) [56].

Genotype 5 or 6, Option 3

- Patients infected with HCV genotype 5 or 6 can be treated with an IFN-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) for 12 weeks **(B1)**
- Based on data with other combinations, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) is recommended in patients with cirrhosis **(B1)**
- In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered **(B1)**

Comments: Daclatasvir is active *in vitro* against both genotype 5 and 6. No data is available with this combination for these rare genotypes.

Treatment monitoring

Treatment monitoring includes monitoring of treatment efficacy and of safety and side effects.

Monitoring of treatment efficacy

Monitoring of treatment efficacy is based on repeated measurements of HCV RNA levels. A sensitive, accurate assay with a broad dynamic range of quantification should be used. The same assay, ideally from the same laboratory, should be used in each patient to measure HCV RNA at different time points, in order to assure consistency of results [57–59].

In order to monitor treatment efficacy, HCV RNA level measurements should be performed at specific time points. Measurements should be made to assess patient adherence to therapy. For some treatment regimens, the HCV RNA level results obtained can determine whether treatment should be abandoned (the futility rule) or abbreviated (response-guided therapy). In all cases, HCV RNA level monitoring indicates whether treatment has been successful (end of treatment and post-treatment SVR assessment). Little is known about the impact of the analytical sensitivity and lower limits of detection or quantification of different HCV RNA assays for assessment of futility rules and determination of treatment duration.

Guidelines

Recommendations

- A real-time PCR-based assay with a lower limit of detection of ≤ 15 IU/ml should be used to monitor HCV RNA levels during and after therapy (**A1**)
- In patients treated with the triple combination of PegIFN- α , ribavirin and sofosbuvir for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy (**A2**)
- In patients treated with the triple combination of PegIFN- α , ribavirin and simeprevir (12 weeks plus 12 or 36 weeks of PegIFN- α and ribavirin alone), HCV RNA should be measured at baseline, week 4, week 12, week 24 (end of treatment in treatment-naïve patients and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy (**A2**)
- In patients treated with an IFN-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment in patients treated 12 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy (**A2**)

Stopping (futility) rules

Futility rules have been defined only with the triple combination of PegIFN- α , ribavirin and simeprevir.

Recommendations

- With the triple combination of PegIFN- α , ribavirin and simeprevir, treatment should be stopped if HCV RNA level is ≥ 25 IU/ml at treatment week 4, week 12 or week 24 (**A2**)
- An immediate switch to another IFN-containing DAA-containing or to an IFN-free regimen without a protease inhibitor should be considered (**B1**)
- No futility rules have been defined for other treatment regimens (**A1**)

Monitoring treatment safety

PegIFN- α -containing regimens

Flu-like symptoms are often present after PegIFN- α injections. They are easily controlled by paracetamol and tend to attenuate after 4–6 weeks of therapy. At each visit, the patients should be assessed for clinical side effects, such as severe fatigue, depression, irritability, sleeping disorders, skin reactions and dyspnoea. Thyroxin and thyroid stimulating hormone (TSH) levels should be measured every 12 weeks while on therapy [60].

Haematological side effects of PegIFN- α and ribavirin include neutropenia, anaemia, thrombocytopenia and lymphopenia. These parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4 to 8 week intervals thereafter.

Ribavirin-containing regimens

Mild anaemia can occur in IFN-free regimens containing ribavirin; indeed, haemoglobin decreases have been greater and more common when DAAs were combined with ribavirin than in regimens without ribavirin.

Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Women of childbearing potential and/or their male partners must use an effective form of contraception during treatment and for a period of 6 months after the treatment has concluded.

Recommendations

- Women of childbearing potential and/or their male partners must use an effective form of contraception during ribavirin-containing treatment and for a period of 6 months after the treatment has concluded (**A1**)

DAA-containing regimens

New DAA regimens are generally well tolerated. Frequencies of high grade or serious adverse events leading to discontinuation of IFN-free regimens are low. However, data in patients with decompensated cirrhosis or in liver transplant recipients are scarce. The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment.

Simeprevir. Patients receiving simeprevir may experience mild to moderate rashes and photosensitivity; sun protection measures and limiting sun exposure is necessary. Indirect hyperbilirubinaemia may occur, but the increment in bilirubin concentrations is less in patients not receiving ribavirin. Patients of East

Asian ancestry exhibit higher simeprevir exposures. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity.

In the COSMOS trial [11], the most common (>10%) adverse reactions reported during 12 weeks treatment with simeprevir in combination with sofosbuvir without ribavirin were fatigue (25%), headache (21%), nausea (21%), insomnia (14%) and pruritus (11%). Rash and photosensitivity were reported in 11% and 7% of subjects, respectively. During 24 weeks treatment with simeprevir in combination with sofosbuvir, dizziness (16%) and diarrhoea (16%) were also commonly reported.

The safety and efficacy of simeprevir has not been studied in HCV-infected patients with severe renal impairment or end-stage renal disease (creatinine clearance below 30 ml/min) or end-stage renal disease, including patients requiring dialysis.

Daclatasvir. The overall safety profile of daclatasvir, either in combination with sofosbuvir with or without ribavirin or in combination with PegIFN- α and ribavirin, suggests that the most common adverse reactions related to this drug are fatigue, headache and nausea.

Sofosbuvir and ledipasvir. The proportion of patients who permanently discontinued treatment due to adverse events during treatment was 0%, <1%, and 1% for patients receiving sofosbuvir and ledipasvir for 8, 12, and 24 weeks, respectively; and <1%, 0%, and 2% for patients receiving sofosbuvir and ledipasvir plus ribavirin combination therapy for 8, 12, and 24 weeks, respectively.

In clinical studies, fatigue and headache were more common in patients treated with sofosbuvir and ledipasvir compared to placebo. When sofosbuvir and ledipasvir were administered with ribavirin, the most frequent adverse drug reactions were consistent with the known safety profile of ribavirin. Renal function should be checked regularly in patients receiving sofosbuvir.

Ritonavir-boosted paritaprevir, ombitasvir, and dasabuvir.

Based on an integrated safety analysis, pruritus, fatigue, nausea, asthenia and insomnia were the most common adverse events encountered in clinical trials with this combination. The more frequent side effects were considered related to ribavirin, but pruritus was considered related to the 3 DAAs regimen. Severe adverse events occurred in <2.5% of cases. Treatment discontinuation due to adverse events occurred in 1–2% per study. Haemoglobin reductions were consistent with ribavirin-induced haemolysis, and largely resolved by post-treatment week 4. Haemoglobin reductions may require ribavirin dose reductions.

Asymptomatic serum ALT elevations generally occurred within the first 4 weeks of treatment, but all resolved without intervention and with continued DAA treatment, none of them being synchronous with bilirubin elevations. Transient increases in indirect serum bilirubin were observed in patients receiving ribavirin, related to the inhibition of bilirubin transporters OATP1B1 and OATP1B3 by paritaprevir and associated haemolysis. A greater frequency of total bilirubin increases was observed in patients with cirrhosis. Oestrogen containing medication use was associated with a greater risk of ALT elevations.

Recommendations

- The patients receiving PegIFN- α and ribavirin should be assessed for clinical side effects at each visit, while the haematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter (**A1**)
- Renal function should be checked regularly in patients receiving sofosbuvir (**B1**)
- Rashes and indirect bilirubin elevations without ALT elevations may be seen with simeprevir (**A1**)
- Indirect bilirubin increases are rarely observed with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (**A1**)
- No dose adjustment of simeprevir, sofosbuvir and ledipasvir or daclatasvir is required in patients with mild, moderate or severe renal impairment. The appropriate dose of sofosbuvir for patients with eGFR <30 ml/min/1.73 m² is not yet established (**B2**)
- No dose adjustment of sofosbuvir plus ledipasvir or daclatasvir is required for patients with mild, moderate or severe (Child-Pugh C) hepatic impairment (**B2**)
- Higher exposures have been observed with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir in patients with severe hepatic impairment and their safety in this group requires further study (**B2**)

Monitoring drug-drug interactions

It is important to review all the drugs taken by the patient, including over the counter preparations and recreational drugs. Also, the following series of questions should be asked: (i) are all the co-administered drugs necessary during the period of HCV treatment (it may be possible to stop a drug, such as a statin, for a period of 8–12 weeks)? (ii) If not, is there an alternative in the same therapeutic class without a drug interaction? Finally, (iii) can a drug interaction be managed either by a change of dose or a clear monitoring plan? For specific drug-drug interactions and dose adjustments, see above.

Recommendations

- The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment (**A1**)
- When possible, an interacting co-medication should be stopped for the duration of HCV treatment or the interacting co-medication should be switched to an alternative drug with less interaction potential (**B1**)

Guidelines

Treatment dose reductions

The PegIFN- α dose should be reduced in case of severe side effects, such as clinical symptoms of severe depression, and if the absolute neutrophil count falls below $750/\text{mm}^3$, or the platelet count falls below $50,000/\text{mm}^3$. When using PegIFN- $\alpha 2a$, the dose can be reduced from $180 \mu\text{g}/\text{week}$ to $135 \mu\text{g}/\text{week}$, and then to $90 \mu\text{g}/\text{week}$. When using PegIFN- $\alpha 2b$, the dose can be reduced from $1.5 \mu\text{g}/\text{kg}/\text{week}$ to $1.0 \mu\text{g}/\text{kg}/\text{week}$ and then to $0.5 \mu\text{g}/\text{kg}/\text{week}$. PegIFN- α should be stopped in case of marked depression, if the neutrophil count falls below $500/\text{mm}^3$ or the platelet count falls below $25,000/\text{mm}^3$. If and when neutrophil or platelet counts rise from those nadir values, treatment can be restarted, but at a reduced dose. IFN treatment interruptions should be as brief as possible. Switch to IFN-free options should be considered in patients who need to stop IFN administration.

If significant anaemia occurs (haemoglobin $<10 \text{ g/dl}$), the dose of ribavirin should be adjusted downward by 200 mg at decrements. A more rapid reduction of dose may be required for patients with rapidly declining haemoglobin, particularly if the baseline haemoglobin was low. Ribavirin administration should be stopped if the haemoglobin level falls below 8.5 g/dl [60–68].

Treatment should be promptly stopped in case of a hepatitis flare (ALT levels above 10 times normal, if not already present at the time of starting treatment) or if a severe bacterial infection occurs at any site, regardless of neutrophil count. Any visual symptoms should be assessed and fundoscopic examination performed during treatment.

No dose adjustments are recommended for sofosbuvir, simeprevir, daclatasvir, sofosbuvir-ledipasvir or ritonavir-boosted paritaprevir/ombitasvir/dasabuvir. Treatment must be stopped in case of severe adverse events, such as sepsis in patients with decompensated cirrhosis. The effects on efficacy and the number of allowable days for pausing treatment, and duration of retreatment in patients who restart after interruption of IFN-free therapy are unknown.

Measures to improve treatment adherence

Full adherence to all drugs is associated with high SVR rates. In contrast, suboptimal exposure to therapy is associated with virological breakthrough or post-treatment relapse and the emergence of resistance-associated variants, especially during the early phase of treatment. Simple measures to enhance adherence to treatment should thus be implemented.

Before starting antiviral therapy, patients must be instructed about the daily schedule and the likely side effects (of both IFN- and ribavirin-containing and IFN-free regimens) to be expected during treatment. Patients should also be instructed about the preventive and therapeutic measures to ameliorate these side effects, for example by using antipyretics, analgesics, or antidepressants if they receive IFN. Regular follow-up visits must be scheduled so that treatment progress and management of side effects can be discussed. Patient recall procedures in cases of missed appointments should be instituted.

The key element of effective HCV clinical management is access to a multidisciplinary team, generally including clinician and nursing clinical assessment and monitoring, virology, drug and alcohol services, HIV infection services, psychiatric support for selected cases, pharmacy, and social work and other social support services (including peer support, if available). Measures

to increase adherence are interdisciplinary. They include HCV education and monitoring services and, particularly, the help of a dedicated nurse [69,70]. For foreign patients, the language and comprehension difficulties should be addressed before starting treatment.

To maximize the likelihood of benefit for patients who begin new HCV treatment regimens, resources should be devoted to patient pretreatment assessment and preparation, as well as to on treatment adherence monitoring and support, which is becoming easier with the new therapeutic regimens.

Alcohol consumption has an impact on treatment adherence [71]. Patients should therefore be advised to stop or to reduce alcohol consumption before start of treatment. Treatment for patients not able to abstain from alcohol should be fitted to the individual, focussing on their ability to adhere to medication and appointments. Hepatitis C patients with on-going alcohol consumption during treatment profit from additional support during antiviral therapy [71–74]. Pharmacists should advise on potential drug-drug interactions.

Recommendations

- HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy (**A1**)
- HCV-infected patients should be counselled on the importance of adherence for attaining an SVR (**A1**)
- In patients with socioeconomic disadvantages and in migrants, social support services should be a component of HCV clinical management (**B2**)
- In persons who actively inject drugs, access to harm reduction programs is mandatory (**A1**)
- Peer-based support should be evaluated as a means to improve HCV clinical management (**B2**)
- Patients should be counselled to abstain from alcohol during antiviral therapy. Patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy (**A1**)
- HCV treatment can be considered also for patients actively using drugs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Also, the potential for drug-drug interactions involving prescribed and non-prescribed drugs needs to be considered (**A1**)

Post-treatment follow-up of patients who achieve an SVR

Non-cirrhotic patients who achieve an SVR should be retested for HCV RNA at 48 weeks post-treatment. If HCV RNA is still not detected, the infection can be considered as definitely cured and HCV RNA need not be retested. As hypothyroidism may occur after stopping IFN therapy, thyroxine and TSH levels should also be assessed 1 and 2 years after treatment if the patient has received IFN. Patients with pre-existing cofactors for liver disease

(notably, history of alcohol drinking and/or type 2 diabetes) should be carefully and periodically subjected to a thorough clinical assessment, as needed.

Cirrhotic patients who achieve an SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pretreatment endoscopy (though first variceal bleed is seldom observed after SVR). The presence of cofactors for liver disease, such as history of alcohol drinking and/or type 2 diabetes, may determine that additional assessments are necessary. The exact duration of HCC surveillance in patients with advanced fibrosis or cirrhosis who achieve an SVR is unknown in the current state of knowledge, but is probably indefinite. Indeed, long-term post-SVR follow-up studies showed that, although it is significantly reduced compared to untreated patients or patients who did not achieve an SVR, the risk of developing HCC remains in patients with cirrhosis who eliminate HCV [2,3]. The level of risk will be determined in prospective studies.

There remains some concern that reinfection due to recurrent or persistent risk behaviour may negate the potential benefit of treatment. Reported rates of reinfection following successful HCV treatment among patients at high risk, such as people who inject drugs or men who have sex with men, are low, with estimates of 1–5% risk per year [75–79]. However the ease of IFN-free therapy may increase the likelihood of reinfection. In order to maximize the benefit of therapy, the risks of reinfection should be emphasized to patients at risk, and behavioural modifications should be positively reinforced.

Recommendations

- Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative **(B1)**
- Cirrhotic patients, and probably also patients with advanced fibrosis (F3), with SVR should undergo surveillance for HCC every 6 months by means of ultrasound **(B1)**
- Guidelines for management of portal hypertension and varices should be implemented, though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for on-going liver damage are present and persist) **(A2)**
- Patients with on-going drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection **(B1)**
- The risk of reinfection should be explained to individuals with on-going risk behaviour, to positively modify risk behaviour **(B1)**
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken in people who inject drugs or men who have sex with men with on-going risk behaviour **(B2)**

Retreatment of non-sustained virological responders

Retreatment of patients who failed after a double combination of PegIFN- α and ribavirin

Several studies indicate that patients who failed to achieve an SVR after treatment with PegIFN- α and ribavirin alone do not respond differently to IFN-free regimens from treatment-naïve patients. Thus, these patients should be retreated with an IFN-free regimen according to the above recommendations (Tables 5 and 6).

Retreatment of genotype 1 patients who failed after a triple combination of PegIFN- α , ribavirin, and either telaprevir or boceprevir (Table 7)

IFN-free treatment regimens have been tested in patients infected with HCV genotype 1 who did not achieve an SVR after treatment with the triple combination of PegIFN- α , ribavirin, and either telaprevir or boceprevir. Experience of retreatment of such patients with the combination of sofosbuvir and simeprevir, with or without ribavirin, for 12 weeks is limited to on-going observational real-life cohorts. In the TARGET 2.0 cohort study, previous failure of triple combination therapy was a significant negative predictor of SVR4 [13]. The role of the presence, at retreatment start, of protease inhibitor resistance-associated variants is unknown. In the TRIO Network real-life study [28], the SVR12 rate with sofosbuvir and simeprevir was 82% (27/33) in patients who failed on triple combination therapy, not different from patients who failed on PegIFN- α and ribavirin alone (80% [60/80]). Retreatment with the combination of PegIFN- α , ribavirin and sofosbuvir of such patients yielded SVR rates of 73% (29/40) and 67% (24/36), respectively [28].

In non-cirrhotic patients who failed on triple combination therapy, 24 weeks of the combination of sofosbuvir and daclatasvir yielded SVR rates of 95% (19/21) and 100% (21/21) without and with ribavirin, respectively [14]. In the ION trial, the SVR rates in patients without cirrhosis retreated with sofosbuvir and ledipasvir for 12 weeks, without or with ribavirin, were 96% (50/52) and 100% (50/51), respectively; they were 97% (35/36) and 100% (38/38) after 24 weeks of therapy without and with ribavirin, respectively [35]. It is noteworthy that in the ION-2 trial, the SVR rates in cirrhotic patients retreated with sofosbuvir and ledipasvir for 12 weeks, without or with ribavirin, were 86% (12/14) and 85% (11/13), respectively; SVR rates increased to 100% (14/14) and 100% (13/13) after 24 weeks of therapy without and with ribavirin, respectively [35]. In the SIRIUS study, the SVR rates with sofosbuvir plus ledipasvir, for either 12 weeks with ribavirin or 24 weeks without ribavirin, were 96% (74/77) and 97% (75/77), respectively [39].

Retreatment of patients who failed after a regimen containing one or more second-wave DAAs (Table 7)

Sofosbuvir has a high barrier to resistance. Clinically meaningful resistant HCV variants have been exceptionally reported with sofosbuvir, and they rapidly disappeared after treatment cessation. Thus, retreatment strategies should include sofosbuvir. In contrast, patients exposed to a protease inhibitor (simeprevir,

Guidelines

paritaprevir), an NS5A inhibitor (daclatasvir, ledipasvir, ombitasvir) or a non-nucleoside inhibitor of HCV polymerase (dasabuvir) who fail to achieve SVR select viruses with amino acid substitutions in the NS3 protease, NS5A and polymerase regions, respectively, that confer drug resistance. Viruses resistant to protease inhibitors and, probably also but more slowly, viruses resistant to non-nucleoside polymerase inhibitors progressively decrease in proportion to become undetectable by means of population sequencing (direct sequence analysis) 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, perhaps forever, after they have been selected by a regimen including an NS5A inhibitor [80–86].

Currently, there is no data to firmly support retreatment recommendations, which must be based on indirect evidence (HCV genotype, known resistance profiles of the administered

drugs, number of drugs used, use of ribavirin, treatment duration). Whether assessing the sequence of the target HCV genes (HCV resistance testing) prior to retreatment is helpful to make a decision remains unknown, as well as which therapeutic decision should be made based on this result.

Intuitively, patients who failed on a DAA-containing regimen should be retreated with an IFN-free combination including a drug with a high barrier to resistance (currently, sofosbuvir), plus one or two other drugs, ideally with no cross-resistance with the drugs already administered. Based on results in difficult-to-cure patient populations, retreatment should be for 12 weeks with ribavirin, or extended to 24 weeks with or without ribavirin (no data available comparing these approaches).

Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus PegIFN- α and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir

Table 7. Treatment recommendations for retreatment of HCV-monoinfected or HCV/HIV coinfecting patients with chronic hepatitis C who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s) RBV: ribavirin.

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
PegIFN- α , RBV and either telaprevir or boceprevir	Genotype 1	12 wk with RBV	No	No	No	12 wk with RBV
	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Sofosbuvir alone, in combination with RBV or in combination with PegIFN- α and RBV	Genotype 2 or 3	No	No	No	No	12 weeks with RBV or 24 weeks with RBV if F3 or cirrhosis
	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN- α , RBV and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
PegIFN- α , RBV and daclatasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Sofosbuvir and simeprevir	Genotype 1 or 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

(continued on next page)

Table 7 (continued)

Failed treatment	Genotype	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Sofosbuvir and daclatasvir or Sofosbuvir and ledipasvir	Genotype 1	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 2 or 3	No	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
	Genotype 4	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No
	Genotype 5 or 6	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir	Genotype 1	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis
Ritonavir-boosted paritaprevir and ombitasvir	Genotype 4	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	No	No	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis	12 wk with RBV or 24 wk with RBV if F3 or cirrhosis

Currently, there is limited data to firmly support these retreatment recommendations, which are based on indirect evidence and consideration of HCV genotype, known resistance profiles of the previously administered drugs, number of drugs used, use of ribavirin, treatment duration. Thus, these recommendations are subject to change when more data become available.

(genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or sofosbuvir plus ledipasvir (genotypes 1, 4, 5 or 6), with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), or with ritonavir-boosted paritaprevir and ombitasvir (genotype 4). In a study, retreatment with 12 weeks of sofosbuvir plus ledipasvir with ribavirin yielded SVR in 98% (50/51) of genotype 1 patients who failed prior treatment with sofosbuvir plus placebo, or sofosbuvir plus ribavirin, or sofosbuvir plus PegIFN- α and ribavirin [87].

Genotype 1 and 4 patients who failed on a regimen combining PegIFN- α , ribavirin and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir. Patients who failed on a regimen combining PegIFN- α , ribavirin and daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4).

Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated

with a combination of sofosbuvir with daclatasvir or ledipasvir, whereas patients who failed on a regimen containing sofosbuvir and daclatasvir or ledipasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4). The retreatment strategy is unclear for patients infected with genotypes 2, 3, 5 or 6 who failed on a regimen containing sofosbuvir and daclatasvir or ledipasvir; retreatment with the same option may be proposed, provided that ribavirin is added and/or treatment duration is extended to 24 weeks.

Patients who failed on the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should be retreated with a sofosbuvir-based regimen. The value and safety of retreatment strategies combining three drugs, including sofosbuvir, a protease inhibitor and an NS5A inhibitor, is unknown.

Patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available.

- Patients who failed after PegIFN- α and ribavirin combination treatment must be retreated like treatment-naïve patients, according to the above recommendations by HCV genotype **(A1)**
- Patients infected with HCV genotype 1 who failed after a triple combination regimen of PegIFN- α , ribavirin and either telaprevir or boceprevir should be retreated with the IFN-free combination of sofosbuvir and ledipasvir, or sofosbuvir and daclatasvir, with ribavirin for 12 weeks **(A1)**
- Recommendations for retreatment after failure of second-wave DAA-based anti-HCV regimens are based on indirect evidence and subject to change when more data become available **(A1)**
- Patients who failed on a second-wave DAA-containing regimen, with or without PegIFN- α , with or without ribavirin, should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin. Extending therapy to 24 weeks with ribavirin may be considered, especially in patients with advanced liver disease, including extensive fibrosis (F3) and cirrhosis (F4) **(B2)**
- Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus PegIFN- α and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir (genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or sofosbuvir plus ledipasvir (genotypes 1, 4, 5 or 6), or with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), or with ritonavir-boosted paritaprevir and ombitasvir (genotype 4) **(B2)**
- Patients infected with HCV genotype 1 or 4 who failed on a regimen combining PegIFN- α , ribavirin and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir **(B2)**
- Patients who failed on a regimen combining PegIFN- α , ribavirin and daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (if they are infected with genotype 1 or 4). Patients infected with other genotypes should be retreated with the combination of sofosbuvir and daclatasvir (genotypes 2, 3, 5 and 6) or with the combination of sofosbuvir and ledipasvir (genotypes 5 and 6) **(B2)**
- Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated with a combination of sofosbuvir with daclatasvir or ledipasvir **(B2)**
- Patients who failed on a regimen containing sofosbuvir and daclatasvir or sofosbuvir and ledipasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4). Patients infected with other genotypes should be retreated with the combination of sofosbuvir and daclatasvir (genotypes 2, 3, 5 and 6) or with the combination of sofosbuvir and ledipasvir (genotypes 5 and 6) for 24 weeks **(B2)**
- Patients infected with genotype 1 who failed on the triple combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir should be retreated with a sofosbuvir-based regimen, e.g. sofosbuvir and simeprevir, sofosbuvir and daclatasvir or sofosbuvir and ledipasvir **(B2)**
- Patients infected with genotype 4 who failed on the double combination of ritonavir-boosted paritaprevir and ombitasvir should be retreated with a sofosbuvir-based regimen, e.g. sofosbuvir and simeprevir, sofosbuvir and daclatasvir or sofosbuvir and ledipasvir **(B2)**
- Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available **(A1)**
- The efficacy and safety of a triple combination regimen including sofosbuvir, an NS3 protease inhibitor and an NS5A protease inhibitor in patients who failed on a DAA-containing regimen is unknown **(B2)**
- The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown **(B2)**

Treatment of patients with severe liver disease

Patients with decompensated cirrhosis without an indication for liver transplantation

The main goal of anti-HCV therapy in patients with decompensated cirrhosis not on a transplant waiting list is to achieve improvement in liver function and survival. A 48-week regimen of sofosbuvir and ribavirin is being assessed in patients with cirrhosis and portal hypertension [88]. Preliminary results demonstrated excellent on treatment responses and slight improvements in liver function tests. The long-term clinical

benefits and the effect of this treatment on portal pressure have not been reported.

A study assessed the safety and efficacy of the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 or 24 weeks in patients with decompensated cirrhosis (Child-Pugh score up to 12) infected with HCV genotype 1 or 4 [89]. The SVR rates were 87% (45/52) and 89% (42/47) after 12 and 24 weeks of treatment, respectively; treatment was equally effective in patients with Child-Pugh B and Child-Pugh C cirrhosis. There was a clear effect of viral clearance on liver function, with significant improvements in bilirubin, albumin and INR values and, as a result, in MELD and Child-Pugh scores. Improvement

of liver function was reported 4 weeks after treatment interruption. It will thus be important to assess the benefit of HCV elimination on liver function and subsequent survival at later time points. These preliminary results suggest that patients with decompensated cirrhosis benefit from this treatment regimen. The treatment indication should take into account the presence of comorbidities that may impact survival. Data in patients with more advanced liver disease (Child-Pugh >12) are limited.

Recommendations

- Patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C, up to 12 points) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival can be treated with the combination of sofosbuvir and ribavirin for 16-20 weeks (genotype 2), the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), or the combination of sofosbuvir and daclatasvir (all genotypes), with weight-based ribavirin, for 12 weeks (**B1**)
- Patients with decompensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B1**)

Patients with HCC without an indication for liver transplantation

HCV is a leading cause of HCC worldwide and the morbidity and mortality from HCV-associated HCC is increasing, especially in high-income areas. HCC occurs at an annual rate of 1–7% in patients with cirrhosis. The risk is related to the severity of fibrosis among other factors. An SVR has been shown to be associated with a reduction in all-cause mortality, liver mortality and a reduction in the risk of HCC. Several metaanalysis have examined the relationship between achievement of SVR and reduction in the risk of HCC, which suggest that SVR is associated with a reduction in HCC [90,91]. However, most of these studies are observational and retrospective and were based on SVR achieved with IFN-based treatments.

As IFN has been shown to improve outcomes following ablation or resection of HCV, it is possible that the high rates of SVR achieved with new IFN-free regimens could reduce the risk of recurrence following resection or ablation of HCC [92]. If the incidence of recurrent HCC can be reduced via this strategy, higher rates of resection or ablation plus an SVR with antiviral treatment could possibly reduce the subsequent need for transplantation for HCV-associated HCC. Further data is required to

evaluate the impact of highly effective IFN-free regimens on the risk of recurrent HCC following resection or ablation.

Recommendations

- Although the long-term benefit of antiviral therapy to reduce the risk of HCC in patients undergoing resection or ablation for HCV-associated HCC is unknown, these patients frequently have advanced fibrosis and should receive appropriate antiviral therapy for their liver disease, following the guidelines above (**B2**)

Patients with an indication for liver transplantation

Liver transplantation is the treatment of choice for patients with end-stage liver disease. However, hepatitis C recurrence due to graft infection is universal after transplantation in the absence of prevention [93], and the life of the graft is reduced in patients with recurrent hepatitis C.

Treatment of HCV infection in patients awaiting a liver transplantation has two complementary goals: preventing liver graft infection after transplantation (in all cases) and improving liver function before transplantation (in patients with decompensated liver disease). It might be argued that as treatment of HCV infection can be achieved in the vast majority of patients after transplantation, there is no need to treat HCV infection prior to transplantation, especially because the duration of antiviral therapy cannot be predicted in a patient on the waiting list. Nevertheless, prevention of liver graft infection substantially facilitates post-transplant management. In addition, improvement of liver function implies delisting of some patients [94], an appropriate strategy in the current context of organ shortage [89]. Also, the risk of HCC recurrence could theoretically be reduced by antiviral therapy after resection; thus, more patients could possibly be offered resection.

In a recently published study [95], 61 patients infected with genotypes 1 or 4 with Child-Pugh A cirrhosis were treated with sofosbuvir and ribavirin up to 48 weeks prior to transplantation; 46 of them were transplanted. The per-protocol efficacy population consisted of 43 patients with an HCV RNA level <25 IU/ml at the time of transplantation. Among them, 30 (70%) had post-transplantation SVR12, meaning no recurrence of infection. The duration of undetectable HCV RNA pre-transplant was the best predictor of response (undetectable HCV RNA for more than 30 continuous days). This proof of concept study demonstrated that an IFN-free regimen administered for a few weeks before transplantation prevented HCV graft infection in a majority of treated patients. In patients infected with genotype 2, the combination of sofosbuvir and ribavirin is the treatment of choice, with very high SVR rates. For other genotypes, this combination should be administered until liver transplantation only if no other treatment choice is available.

Guidelines

Treatment with PegIFN- α , ribavirin and sofosbuvir for 12 weeks is acceptable in patients with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation if IFN-free combinations are not available, based on a study in 164 genotype 1-infected patients, half treatment-experienced and one-third with cirrhosis, who achieved SVR4 in 85% of cases [13].

The combination of sofosbuvir and ledipasvir with ribavirin for 12 or 24 weeks was assessed in genotype 1 and 4 patients with compensated (Child-Pugh A) or decompensated (Child-Pugh B and C, up to 12 points) cirrhosis [89]. In Child-Pugh A patients, data from this and other studies showed SVR12 rates above 95%, both in treatment-naïve and treatment-experienced individuals, independent of treatment duration. In patients with decompensated cirrhosis, preliminary analysis showed SVR12 rates of 88% (50/57) and 88% (37/42) in Child-Pugh B and C patients, respectively, independent of treatment duration [89]. At week 4 post-treatment, the MELD scores had improved by 1 to 8 points in 64% (34/53) of Child-Pugh B patients and in 70% (28/40) of Child-Pugh C patients. Child-Pugh scores improved by 1 to 3 points in approximately two-thirds of patients. The safety profile of this combination was good and most serious adverse events, including death, were unrelated to the study drugs. Although the study was not specifically designed to assess the impact of antiviral therapy in patients awaiting liver transplantation, the data support the use of this combination in patients with compensated and decompensated cirrhosis on the waiting list.

Data on the efficacy and safety of the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin in compensated cirrhotic patients infected with genotype 1 have been published [45]. Patients with compensated cirrhosis awaiting liver transplantation typically have more advanced liver disease and portal hypertension than those included in this study; however, patients with low albumin levels (<35 g/dl, 43 patients) and low platelet counts (<100,000 cells/ml, 78 patients) were included. In patients with a platelet count <100,000 cells/ml, the SVR12 rates were 89% and 97% in the 12- and 24-week treatment duration arms, respectively. The SVR rates in patients with an albumin level <35 g/dl were 84% and 89%, respectively. Thus, this combination can be considered in individuals with compensated cirrhosis and HCC who are on the waiting list.

The combination of sofosbuvir and simeprevir, with or without ribavirin, has been assessed in large real-life cohorts including a significant number of patients with cirrhosis [13]. In patients with HCV genotype 1 infection and compensated cirrhosis, the SVR4 rates were in the order of 90%. Preliminary data in 81 genotype 1-infected patients with decompensated cirrhosis showed an SVR4 rate of 75%, with a good safety profile. However, simeprevir is not indicated in patients with decompensated cirrhosis, due to the higher drug concentrations observed.

Recommendations

- In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection **(A1)**
- Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation and assess the effect of viral clearance on liver function, because significant improvement in liver function may lead to delisting selected cases **(B1)**
- Patients awaiting liver transplantation should be treated with an IFN-free regimen, in principle for 12 or 24 weeks, practically up to transplantation, with ribavirin **(A1)**
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC can be treated with the combination of sofosbuvir and ribavirin for 16–20 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a), with the combination of ritonavir-boosted paritaprevir and ombitasvir with ribavirin for 12 weeks (genotype 4), with the combination of sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes) **(B1)**
- Treatment with PegIFN- α , ribavirin and sofosbuvir for 12 weeks is acceptable in patients with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation if IFN-free combinations are not available **(B2)**
- Patients with decompensated cirrhosis (Child-Pugh B or C) awaiting liver transplantation can be treated with the combination of sofosbuvir and ribavirin for 16–20 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes); however, data are limited in patients with Child-Pugh C cirrhosis >12 points or with a MELD score >20 **(A1)**
- The optimal timing of treatment (i.e. before transplantation or post-transplantation) to maximize survival is still debatable and requires individual assessment **(B2)**
- Due to the limited amount of safety data reported in patients with decompensated cirrhosis awaiting liver transplantation, frequent clinical and laboratory assessment is necessary **(B2)**

Post-liver transplantation recurrence

HCV infection recurrence is universal in patients with detectable HCV RNA at the time of liver transplantation [93]. The course of HCV-related liver disease is accelerated in liver transplant recipients and approximately one-third of them develop cirrhosis within 5 years following transplantation [96,97]. Patients with acute cholestatic hepatitis and patients with moderate to extensive fibrosis or portal hypertension one year after transplantation are at high risk of graft loss, and must urgently receive antiviral therapy [98,99].

Treatment with PegIFN- α and ribavirin yields low SVR rates and is poorly tolerated in liver transplant recipients. The addition of telaprevir or boceprevir increases the SVR rates to 60–70% in patients infected with genotype 1, but at the cost of frequent severe adverse events. Moreover, adjustments in the doses of calcineurin inhibitors are necessary to avoid toxicity due to drug-drug interactions. Nevertheless, HCV clearance has been shown to have a positive impact on both graft and patient survival [100,101].

The first study assessing the safety and efficacy of an IFN-free regimen in HCV-infected liver transplant recipients used a combination of sofosbuvir and ribavirin for 24 weeks [102]. The cohort included 40 patients, of whom 40% had cirrhosis and 88% were non-responders to an IFN-based treatment. This regimen yielded an SVR12 rate of 70%, with an excellent safety profile (severe adverse events in 15% of patients, anaemia in 20% and treatment discontinuations in 5%). Calcineurin inhibitor dose adjustments were not required due to the lack of significant interactions of sofosbuvir with tacrolimus or cyclosporine. The beneficial impact of HCV clearance on liver function and patient survival post-liver transplantation is supported by data from the sofosbuvir compassionate use program, which included patients with severe hepatitis C recurrence and a life expectancy without antiviral therapy of less than 12 months [103]. Patients received up to 48 weeks of sofosbuvir and ribavirin, with or without PegIFN- α . The SVR12 rate was 59%. Fifty-seven percent of patients had a significant clinical improvement at the last study visit, whereas 22% were unchanged, 3% had worsened their clinical status and 13% died. These results suggest that HCV clearance impacts survival in these very sick patients, particularly those with severe early recurrence. In real-life patients infected with genotype 2, the combination of sofosbuvir and ribavirin post-liver transplant yielded a very high SVR rate in the TARGET study [13].

Preliminary data from an on-going clinical trial assessing the efficacy and safety of the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 or 24 weeks were presented [104]. The patients included treatment-naïve and mostly treatment-experienced patients with genotype 1 or 4 infection, with all fibrosis stages (F0 to F4) including patients with Child-Pugh B and C decompensated cirrhosis. The SVR rates were 97% (108/111) in F0-F3 patients, 96% (49/51) in Child-Pugh A patients, and 84% (37/44) in Child-Pugh B patients. Data were available in only 8 Child-Pugh C patients, 5 of whom (62%) achieved an SVR. There were no differences in efficacy between 12 and 24 weeks of therapy and the combination had an excellent safety profile. As in immunocompetent patients, MELD scores at week 4 post-treatment improved in the majority of Child-Pugh A and B patients who achieved viral clearance [104].

The antiviral efficacy and safety of the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 24 weeks was tested in 34 HCV genotype 1 liver transplant recipients [105]. All of them were treatment-naïve post-transplantation and had F0 to F2 fibrosis. All but one achieved SVR12, while only 6% of patients reported severe adverse events, 17% anaemia, and 1 patient had to discontinue therapy. Due to drug-drug interactions with ritonavir and paritaprevir, tacrolimus or cyclosporine dose adjustments were required during the treatment period. In patients with more advanced liver disease, data must be extrapolated from patients not in the post-transplant recurrence setting.

Data from real-life cohorts with a combination of sofosbuvir and simeprevir with or without ribavirin for 12 weeks were reported. SVR12 was achieved in 91% (60/66) of patients infected with genotype 1, most of whom were treatment-experienced with one-third having advanced fibrosis or compensated cirrhosis. The SVR rate was slightly lower in genotype 1a patients with advanced fibrosis [28]. In the TARGET real-life cohort study, in which most patients were treatment-experienced and more than half had cirrhosis, the combination of sofosbuvir and simeprevir yielded a 90% (61/68) SVR4 rate [106].

Little data is available with the combination of sofosbuvir and daclatasvir in the post-transplant setting, mostly from small real-life cohorts. Overall, SVR is achieved in more than 90% of cases, including in patients with fibrosing cholestatic hepatitis [107], with this well tolerated regimen.

Guidelines

Recommendations

- All patients with post-transplant recurrence of HCV infection should be considered for therapy **(A1)**
- Acute cholestatic hepatitis or the presence of moderate to extensive fibrosis or portal hypertension one year after transplantation predict rapid disease progression and graft loss and indicate more urgent antiviral treatment **(A1)**
- Patients with post-transplant recurrence of HCV should be treated with an IFN-free regimen, for 12 or 24 weeks with ribavirin **(A1)**
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis post-transplant can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes), without the need for immunosuppressant drug dose adjustments **(A1)**
- Patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis post-transplant can be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a with cirrhosis), with the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 or 24 weeks with ribavirin (genotype 4 without or with cirrhosis, respectively), or with the combination of sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), with the need for immunosuppressant drug dose adjustments or, in the case of the sofosbuvir-simeprevir combination, the need to avoid cyclosporine A **(B1)**
- Patients with decompensated (Child-Pugh B or C) cirrhosis can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with the fixed-dose combination of sofosbuvir and ledipasvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with the combination of sofosbuvir and daclatasvir with ribavirin for 12 weeks (all genotypes). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance **(B1)**
- No dose adjustment is required for tacrolimus or cyclosporine with sofosbuvir-ribavirin, sofosbuvir-ledipasvir or sofosbuvir-daclatasvir **(A2)**
- Because of significantly increased plasma concentrations of simeprevir, the concomitant use of simeprevir and cyclosporine A is not recommended in liver transplant recipients. No simeprevir dose changes are required with tacrolimus and sirolimus, but regular monitoring of their blood concentrations should be performed **(A2)**
- When using the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir, the tacrolimus dose must be adjusted to 0.5 mg once weekly or 0.2 mg every 3 days, while cyclosporine A dose must be adjusted to one-fifth of the daily dose given prior to HCV treatment once daily; prednisone use at doses ≤ 5 mg/day is permitted, but the use of mTOR inhibitors is not recommended **(A2)**

Treatment of special groups

HBV coinfection

In patients with HCV-HBV coinfection, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of chronic hepatitis activity. Patients should be carefully characterized for the replicative status of both HBV and HCV, and hepatitis delta virus infection should be sought. When HCV is replicating and causes liver disease, it should be treated following the same rules as applied to HCV monoinfected patients. There is a potential risk of HBV reactivation during or after HCV clearance [108]. In that case, or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. Simeprevir increases exposure to tenofovir. Thus, in patients receiving tenofovir as anti-HBV treatment, the eGFR and tubular function should be monitored frequently during treatment and tenofovir doses should be consequently adjusted.

Recommendations

- Patients should be treated with the same regimens, following the same rules as HCV monoinfected patients **(B1)**
- If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated **(B1)**

Immune complex-mediated manifestations of chronic hepatitis C

Several severe systemic immune complex-mediated manifestations of chronic HCV infection have been described. Mixed cryoglobulinemia underlain by B lymphocyte expansion

may cause a systemic vasculitis in which multiple organs are involved as a result of vascular deposition of immune complexes. The treatment of mixed cryoglobulinemia relies on causal (antiviral) therapy and/or immunosuppressive therapy. Rituximab, an anti-CD20 monoclonal antibody, has been used for both skin and organ involvement.

There is a significant association between hepatitis C and B cell non-Hodgkin lymphoma. Diffuse large B cell lymphoma is the most common. The disease is treated with standard of care R-CHOP regimens; the outcome with rituximab appears to be enhanced albeit that rituximab may enhance viral replication. Rituximab has been associated with the possibility of hepatic toxicity and transaminase elevations although the risk is low.

The association of chronic HCV infection and chronic renal disease is well-established. A spectrum of histopathological lesions has been reported but the most frequent is type I membranoproliferative glomerulonephritis, usually in the context of type II mixed cryoglobulinemia. Focal segmental glomerulosclerosis, vasculitic involvement and interstitial nephritis may also occur. Approaches to therapy of HCV-associated renal disease include antiviral therapy, corticosteroids and cyclophosphamide, B cell depletion therapy to prevent the formation of immune complexes, or plasma exchange. It is possible but unproven that the more effective and rapid antiviral response observed with new IFN-free antiviral regimens will improve outcome. Some evidence for rituximab in the management of HCV-induced renal disease exists. However, there are questions regarding its safe and optimal use together with rapidly acting DAAs that need to be addressed. An interdisciplinary approach is recommended.

Recommendations

- Treatment of HCV-associated lymphoma should utilise new IFN-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known. The effect of new antiviral therapies together with B cell depletion requires further study. An interdisciplinary approach with close monitoring of liver function is required (**B1**)
- Appropriate antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection. The role of rituximab in HCV-related renal disease requires evaluation. The more rapid inhibition of HCV replication and high SVR rates will need correlation with the response of the renal injury and the cryoglobulinemia. Careful monitoring for adverse events is mandatory (**B1**)

Patients with comorbidities

Haemodialysis patients.

HCV infection is prevalent in the haemodialysis population and is associated with an increased risk for all-cause and liver-related mortality. Cardiovascular disease remains, however, the main

cause of death in dialysis patients irrespective of HCV status. As in all settings, the candidacy of a dialysis patient for antiviral therapy requires special consideration of co-morbid conditions, since the liver disease may have little impact on predicted morbidity and mortality of that patient. HCV-associated liver damage may be accelerated by immunosuppression. For this reason, antiviral therapy should be considered for all haemodialysis patients who will be candidates for renal transplantation.

The use of ribavirin is problematic in this setting. Individualized ribavirin dosing of 200 mg/day or 200 mg/every other day or 200 mg thrice weekly after haemodialysis is recommended, and substantial hematopoietic support is essential. There are no published data to describe the pharmacokinetics, dosing safety and efficacy of current IFN-free anti-HCV regimens in haemodialysis patients. This is an urgent unmet need.

Recommendations

- Haemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy (**B1**)
- Haemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis (**B1**)
- Simeprevir, daclatasvir, and the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease (**A1**)
- Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m² or with end-stage renal disease until more data is available (**B2**)
- The need for dose adjustments for the approved HCV DAAs in patients on dialysis is unknown. No safety dosing and efficacy data is available in this population. These drugs should thus be used with extreme caution in patients with severe renal disease, and only in extreme life-threatening situations for patients on dialysis (**B1**)

Non-hepatic solid organ transplant recipients

HCV infection in kidney transplant recipients may be associated with an increased rate of liver fibrosis progression. Most studies of kidney transplant cohorts show that HCV positivity is associated with impaired renal graft and patient survival. Impaired graft survival partly reflects increased patient mortality. In addition, specific HCV-related causes such as glomerulonephritis and increased risk of diabetes will affect graft outcome. HCV positivity is associated with increased all-cause and liver-related mortality, though cardiovascular disease remains the main cause of patient death [109]. As cirrhosis is an important predictor of poor post-transplant survival after kidney transplantation, it is advisable to assess the stage of liver fibrosis in all HCV-positive kidney

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transplant candidates [94]. For patients with established cirrhosis and portal hypertension who fail (or are unsuitable for) HCV antiviral treatment, isolated renal transplantation may be contra-indicated and consideration should be given to combined liver and kidney transplantation [110]. As IFN-based treatment may lead to graft rejection, there is an urgent need to offer these patients IFN-free regimens. It remains to be determined whether patients with chronic hepatitis C without cirrhosis should optimally proceed to renal transplantation, with the expectation that their hepatitis C can be cured post-transplant to improve the outcome.

Data on HCV infection after heart transplantation are scarce and controversial, with studies showing unaltered or decreased survival rates in patients infected with HCV. No studies on the risks and benefits of antiviral therapy are available in these patients and the risk of graft rejection on IFN- α treatment remains unclear. In this context, treatment of chronic HCV infection in heart transplant recipients must be based on IFN-free regimens and the indication should be assessed on a case-by-case basis, if HCV infection is life-threatening.

International guidelines list chronic HCV infection as a contra-indication to lung transplantation [111]. Treatment of lung transplant candidates before transplantation has been recommended by some authors, but there is limited experience with this approach. No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

Recommendations

- HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. Where possible, antiviral therapy should be given to potential transplant recipients before listing for renal transplantation. These patients should receive an IFN-free, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with compensated (Child-Pugh A) cirrhosis, following the above recommendations. However, no safety and efficacy data is available in this population, and the need for dose adjustments for the new DAAs is unknown. These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m² or with end-stage renal disease until more data is available (**B1**)
- In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an IFN-free regimen, following the above recommendations on treatment regimen and management of drug-drug interactions with cyclosporine and tacrolimus when appropriate (**B2**)

Active drug addicts and patients on stable maintenance substitution
Ageing cohorts of people who inject drugs (PWID) with chronic HCV and low treatment uptake are making a significant contribution to the population with advanced liver disease and to liver-related mortality [112,113]. The prevalence of HCV among PWIDs is approximately 65% [114–116] and >80% among long-term PWIDs [114].

HCV treatment must be considered for PWIDs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Guidelines for pre-therapeutic assessment for HCV-infected individuals are available [5,117]. Modelling studies suggest that implementation of HCV treatment for PWIDs could reduce transmission [118,119]. Decisions to treat must be made on a case-by-case basis. PWIDs with on-going social issues and/or with a history of psychiatric disease or with more frequent drug use during therapy are at risk of lower adherence and reduced likelihood of achieving SVR and need to be monitored closely during therapy, and also need more supporting measures.

HCV treatment has been delivered successfully to drug users through various clinical models, including within general hospital liver disease and viral hepatitis clinics, drug detoxification clinics, opioid substitution therapy clinics, prisons and community-based clinics. Strategies to enhance treatment adherence were discussed above.

DAA clinical development programs have excluded individuals with active drug use, but many trials have included those on opioid substitution therapy. DAA-based safety and treatment outcome data has not been presented on clinical trial sub-populations of individuals on opioid substitution therapy. Drug-drug interaction studies have been undertaken with sofosbuvir and simeprevir on the one hand, methadone [120] and buprenorphine [121] on the other hand, with no clinically important interactions observed. Interaction studies with daclatasvir and methadone/buprenorphine are underway.

In addition to opioid substitution therapy, antidepressants, antipsychotics and sedatives are frequently used in patients or used by patients with addiction problems. No significant drug-drug interaction has been reported with sofosbuvir. Simeprevir increases blood concentrations of orally administered midazolam and potentially triazolam. Caution is thus warranted when these drugs with a narrow therapeutic index are co-administered via the oral route. Little data is available with daclatasvir. Pharmacokinetic studies on recreational and illicit drug use have not been performed.

Recommendations

- PWIDs should be routinely and voluntarily tested for HCV antibodies and if negative, every 6-12 months **(B1)**
- PWIDs should be provided with clean drug injecting equipment and access to opioid substitution therapy as part of widespread comprehensive harm reduction programs, including in prisons **(B1)**
- Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies **(B1)**
- PWIDs should be counselled to moderate alcohol intake, or to abstain if there is evidence of advanced liver disease **(A1)**
- PWIDs should be counselled to moderate cannabis use, or to abstain if there is evidence of advanced liver disease **(B2)**
- HCV treatment for PWIDs should be considered on an individualized basis and delivered within a multidisciplinary team setting **(A1)**
- Pre-therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition and drug and alcohol use. PWIDs should be linked into social support services and peer support, if available **(A1)**
- A history of intravenous drug use and recent drug use at treatment initiation are not associated with reduced SVR and decisions to treat must be made on a case-by-case basis **(B1)**
- Drug and alcohol users or any other patients with ongoing social issues and/or history of psychiatric disease, and those with more frequent drug use during therapy, are at risk of lower adherence and reduced likelihood of achieving SVR. They need to be monitored more closely during therapy and need more intensive multidisciplinary support **(B1)**
- Evaluation of safety and efficacy of new IFN-containing and IFN-free regimens in PWIDs is needed **(C1)**
- PWIDs on opioid substitution therapy should receive an IFN-free regimen **(B1)**
- The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir **(B1)**
- Awareness should be raised that liver transplantation is a therapeutic option in those with a history of intravenous drug use **(B1)**
- Opioid substitution therapy is not a contra-indication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy **(B1)**

Haemoglobinopathies

The most frequent haemoglobinopathy associated with chronic hepatitis C is thalassemia major, which requires frequent blood transfusions and is prevalent in countries where blood supply screening may be, or has been, suboptimal. Chronic HCV infection is also frequent in individuals with sickle cell anaemia. Treatment has often been withheld in these patients because both PegIFN- α and ribavirin can cause anaemia. No trials with antiviral therapy have been published in this population, but trials are in progress. In the absence of published studies to examine the safety of IFN-free treatment regimens in patients with haemoglobinopathies, there is no reason to consider that these drugs are specifically contra-indicated. Thus, IFN-free, ribavirin-free drug regimens should be used in these patients because they have the great advantage of not aggravating the anaemia.

Recommendations

- The indications for HCV therapy are the same in patients with and without haemoglobinopathies **(A1)**
- Patients with haemoglobinopathies should be treated with an IFN-free regimen, without ribavirin **(B1)**
- The anti-HCV regimens that can be used in patients with haemoglobinopathies are the same as in patients without haemoglobinopathies **(B1)**
- When the use of ribavirin is needed, careful monitoring is recommended, and blood transfusions may be required **(B2)**

Bleeding disorders

Haemophilia is an inherited bleeding disorder caused by a deficiency of either factor VIII or IX in haemophilia A and B, respectively. Patients suffer spontaneous and traumatic bleeds. Treatment is based on intravenous replacement of these factors which, until recently, were prepared from plasma donations. Clotting factor concentrates are prepared from pools of plasma containing up to 30,000 donations and prior to 1985 were infused into recipients without any viral inactivation. Haemophiliacs exposed to non-virally inactivated concentrates prior to 1985 had an almost 100% chance of being infected with HCV with their first exposure to concentrate. There are a number of other inherited bleeding disorders treated with concentrates, including von Willebrand disease, and deficiencies of fibrinogen and factors II, VII, X, XI, and XIII.

Progression to end-stage liver disease in patients with haemophilia is similar to HCV-positive individuals in the general population. The investigation of chronic liver disease in haemophilia is the same as in non-haemophilic individuals. Transjugular liver biopsies have enhanced the safety of the procedure. Non-invasive methods can be utilised to monitor disease progression. Death from liver failure in HCV-positive individuals is among the commonest causes of death in patients with inherited bleeding disorders. With the exception of unavailability of liver histology, the management of chronic hepatitis C in haemophilia is similar to the non-haemophilic population. New HCV DAAs are applicable to patients with haemophilia.

Guidelines

Over 100 liver transplants have been carried out in haemophilic patients worldwide. Factor VIII/IX concentrate is administered immediately before the surgery, either by bolus injection or continuous infusion, and for the immediate post-operative period for 12–48 h, after which no further concentrate is required. Coinfection with HIV/HCV is not a contra-indication to liver transplantation in haemophilia. The indications for liver transplantation in humans with haemophilia are the same as non-haemophilic individuals, but the procedure has the major advantage of producing a phenotypic cure of the haemophilia as a result of factor VIII production by the transplanted liver.

Recommendations

- The indications for HCV therapy are the same in patients with and without bleeding disorders **(A1)**
- Potential drug-drug interactions in HCV-HIV coinfecting patients receiving antiretroviral agents requires careful selection of agents **(A1)**

Follow-up of untreated patients and of patients with treatment failure

Untreated patients with chronic hepatitis C and those who failed to respond to previous treatment should be regularly followed. The reason(s) for non-treatment and treatment failure should be clearly documented. Untreated patients should be assessed every 1 to 2 years with a non-invasive method. Patients with cirrhosis should undergo specific surveillance for HCC every 6 months.

Recommendations

- Untreated patients with chronic hepatitis C and those who failed prior treatment should be regularly followed **(A1)**
- Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals **(A1)**
- HCC surveillance must be continued indefinitely in patients with cirrhosis **(A1)**

Treatment of acute hepatitis C

Most patients with acute hepatitis C are asymptomatic, but a high rate of chronicity is expected without treatment (50–90%). Symptomatic disease with jaundice, female gender, a young age, and genetic polymorphisms in the region upstream of the *IL28B* gene have been associated with spontaneous viral clearance, but none of these parameters accurately predicts spontaneous resolution at the individual level.

Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic

hepatitis C. High SVR rates (>90%) have been reported with PegIFN- α monotherapy, regardless of the HCV genotype. Lower SVR rates have been reported with this regimen in patients with HIV coinfection. Combination therapy with ribavirin does not increase the SVR rate in HCV-monoinfected patients, but used to be considered during treatment in patients with slow response, HIV coinfection and other negative predictors of treatment response [122–130]. A study reported higher SVR rates after the addition of telaprevir to PegIFN- α and ribavirin in HIV-coinfecting patients infected with genotype 1 [131]. No data are available on the use of new IFN-free treatment regimens in patients with acute hepatitis C.

The ideal time point for starting therapy has not been firmly established. Some investigators estimate that the onset of ALT elevation, with or without clinical symptoms, may be the ideal time point for treatment [132–135]. It has also been suggested that patients should be followed with 4-weekly HCV RNA quantification and that only those who remain HCV RNA positive at 12 weeks from onset should be treated [136].

Recommendations for treatment of patients with acute hepatitis C can only be inferred from results obtained *a priori* more difficult-to-cure chronically infected patients. There is currently no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission.

Recommendations

- Based on existing data, PegIFN- α monotherapy (PegIFN- α 2a, 180 μ g/week or PegIFN- α 2b, 1.5 μ g/kg/week) for 12 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases **(A1)**
- PegIFN- α (PegIFN- α 2a, 180 μ g/week or PegIFN- α 2b, 1.5 μ g/kg/week) should be combined with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or \geq 75 kg, respectively) for 24 weeks in patients with acute hepatitis C who are HIV-coinfecting **(B1)**
- Although no data is available yet, IFN-free regimens can be used in these patients as they are expected to achieve high SVR rates. The same doses and durations as for patients with chronic hepatitis C can be used, without ribavirin, until new data indicate whether shorter and/or less intensive treatment is sufficient to achieve high infection cure rates **(B1)**
- There is no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission **(B1)**

Perspective of new treatments

Other treatment regimens are at the clinical developmental stage and could reach the market within the next few years. They include nucleotide analogue-based regimens; nucleotide-free triple combinations of three drugs, each with a low barrier to resistance, which collectively achieve a high barrier to resistance; and nucleotide-free double combinations of two drugs that include at

least one “second-generation” drug with a higher barrier to resistance [137,138]. New pangenotypic agents with greater potency and a higher barrier to resistance will be required to offset drug resistance associated with treatment failures as treatment is expanded. Thus, these recommendations will be updated regularly, following approval of new drug regimens by the European Medicines Agency.

Conflict of interest

Jean-Michel Pawlotsky: Grant and research support: Gilead. Advisory Boards: Abbvie, Achillion, Bristol-Myers Squibb, Gilead, Janssen, Merck. Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Roche.

Alessio Aghemo: Advisory Boards: Abbvie, Gilead, Janssen, and Merck. Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Roche.

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