Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2016☆

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 180 million [2], but most are unaware of their infection. 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.

The primary goal of HCV therapy is to cure the infection, i.e. to achieve a sustained virological response (SVR) defined as undetectable HCV RNA 12 weeks or 24 weeks after treatment completion. The infection is cured in more than 99% of patients who achieve an SVR. An SVR is generally associated with normalization of liver enzymes and improvement or disappearance of liver necroinflammation and fibrosis in patients without cirrhosis. Patients with severe liver disease 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 [3–5]. HCV is also associated with a number of extrahepatic manifestations and effective viral suppression induces reversal of most of them [6].

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 by the European Medicines Agency and other national European agencies at the time of their publication.

Received 9 September 2016; accepted 9 September 2016

☆ ***Coordinator:*** Jean-Michel Pawlotsky; ***Panel members:*** Alessio Aghemo, David Back, Geoffrey Dusheiko, Xavier Forns, Francesco Negro, Massimo Puoti, Christoph Sarrazin.

* Correspondence: EASL Office, 7 rue Daubin, CH 1203 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724.
E-mail address: easloffice@easloffice.eu

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' personal experiences and opinion. Wherever 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 [7]. 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 and other national European agencies.

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 $\leqslant$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 [8,9].

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 (alanine aminotransferase [ALT] >10 times the upper limit of normal, and jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

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

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.

HCV reinfection has been described after spontaneous or treatment-induced HCV clearance, essentially in patients at high-risk of infection. Reinfection is defined by the reappearance of HCV RNA at least 6 months after an SVR and the demonstration that infection is due to a different HCV strain (different genotype or distantly related strain by phylogenetic analysis if the genotype is the same).

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 [10], the diagnosis of chronic hepatitis C can be made after that time period.

HCV core antigen is a surrogate marker of HCV replication. Core antigen detection can be used instead of HCV RNA detection to diagnose acute or chronic HCV infection. HCV core antigen assays are less sensitive than HCV RNA assays (lower limit of detection equivalent to approximately 500 to 3000 HCV RNA IU/ml, depending on the HCV genotype [11,12]). As a result, HCV core antigen becomes detectable in peripheral blood a few days after HCV RNA in patients with acute hepatitis C. In rare cases, core antigen is undetectable in the presence of HCV RNA.

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 3 months later to confirm definitive clearance (**A1**).
- HCV core antigen is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication) (**A1**).

Screening for chronic hepatitis C

A major barrier to HCV elimination still results from the fact that a substantial proportion of patients with chronic hepatitis C are unaware of their infection, with large variations across the different regions/countries. 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 screening for markers of HCV infection must be implemented.

Different screening strategies have been implemented in different regions, based on the local epidemiology. Groups at higher risk of HCV infection can be identified and should be tested. In regions where the majority of patients belong to a well-defined age group, birth cohort testing proved efficacious, with limitations [13,14]. Systematic one-time testing has been recommended in countries with high endemicity and/or a goal of complete eradication. However, the optimal regional or national screening approaches should be determined.

Screening for HCV infection is based on the detection of anti-HCV antibodies. In addition to EIAs, rapid 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 [15–17]. Dried blood spots can also be used to collect whole blood specimens in order to perform EIA detection of anti-HCV antibodies in a central laboratory [18–20].

Recommendations

- Screening strategies for HCV infection should be defined according to the local epidemiology of HCV infection, ideally within the framework of national plans (**A1**).
- Screening for HCV infection is presently based on the detection of anti-HCV antibodies (**A1**).
- Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture (**A1**).
- Rapid diagnostic tests using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical enzyme immunoassays to facilitate anti-HCV antibody screening and improve access to care (**A1**).
- If anti-HCV antibodies are detected, HCV RNA, or alternatively HCV core antigen if HCV RNA assays are not available or not affordable, should be determined to identify patients with on-going infection (**A1**).

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

JOURNAL OF HEPATOLOGY

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 extrahepatic diseases, including hepatic necroinflammation, fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death.

The endpoint of therapy is an SVR, defined by undetectable HCV RNA in blood 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 $\leqslant$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% [21]. Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases [22]. Undetectable HCV core antigen 12 or 24 weeks after the end of therapy can be used as an alternative to HCV RNA testing to assess the SVR12 or the SVR24, respectively, in patients with detectable core antigen before treatment [11,12,23,24].

Recommendations

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death (**A1**).
- The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment (**A1**).
- Undetectable HCV core antigen 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment is an alternative endpoint of therapy in patients with detectable HCV core antigen prior to therapy if HCV RNA assays are not available or not affordable (**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**).

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 and therapeutic choices, should be systematically investigated. 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, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (for instance genetic hemochromatosis, diabetes mellitus 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 (bridging) fibrosis is of particular importance, as the choice of the treatment regimen and the post-treatment prognosis depend on the stage of fibrosis. Assessment of the stage of fibrosis is not required in patients with clinical evidence of cirrhosis. Patients with cirrhosis need assessment of portal hypertension, including oesophageal varices. Patients with advanced fibrosis (METAVIR score F3) and those with cirrhosis need on-going surveillance for HCC every six months. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT levels.

In chronic hepatitis C, considerable evidence suggests that non-invasive methods can 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 and the presence of portal hypertension 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 [25].

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 [26,27]. 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 coinfection, metabolic syndrome, alcoholism or autoimmunity).

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 treatment regimen and post-treatment surveillance must 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**).
- Cardiac and renal function should be ascertained (**A1**).

HCV RNA or HCV core antigen detection/quantification

HCV RNA detection/quantification is indicated for the patients 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.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Table 2. Clinically relevant resistance-associated substitutions (RASs), i.e. RASs which, when detected at baseline by means of either population sequencing or deep sequencing with a cut-off of 15%, may influence the choice of first-line treatment regimen.

NS5A amino acid position	Ledipasvir RASs Genotype 1a Sofosbuvir/ Ledipasvir treatment	Elbasvir RASs Genotype 1a Grazoprevir/ Elbasvir treatment	NS5A RASs Genotype 3 Sofosbuvir/ Velpatasvir treatment
M28	M28A M28G M28T	M28A M28G M28T	
Q30	Q30E Q30G Q30H Q30K Q30R	Q30D Q30E Q30G Q30H Q30K Q30L Q30R	
L31	L31M L31V	L31F L31M L31V	
P32	P32L P32S		
H58	H58D	H58D	
Y93	Y93C Y93H Y93N Y93S	Y93C Y93H Y93N Y93S	Y93H

HCV core antigen detection and quantification by means of EIA can be performed when HCV RNA tests are not available or not affordable. HCV core antigen quantification should be made with a reliable assay and core antigen levels should be expressed in fmol/L.

HCV genotype determination

The HCV genotype, including genotype 1 subtype (1a or 1b), should be assessed prior to treatment initiation. Genotyping/subtyping should be performed with an assay that accurately discriminates subtype 1a from 1b, i.e. an assay using the sequence of the 5′ untranslated region plus a portion of another genomic region, generally the core-coding or the NS5B-coding regions [28].

HCV resistance testing

No standardized tests for the resistance of HCV to approved drugs are available as purchasable kits. Resistance testing relies on in-house techniques based on population sequencing (Sanger sequencing) or deep sequencing [29]. A limited number of laboratories have made such tests available in Europe and in other continents. HCV resistance testing may be technically difficult, in particular for genotypes other than 1 and 4, and the performances of the available in-house assays widely vary. Thus, access to HCV resistance testing remains limited.

Because access to reliable HCV resistance testing is limited and there is no consensus on the techniques or the interpretation and the reporting of these tests, systematic testing for HCV resistance prior to treatment is not recommended [30]. Indeed, systematic testing would seriously limit access to care, whereas treatment can be optimized for groups of patients with the risk that the presence of resistance-associated substitutions (RASs) at baseline reduces response to therapy.

Physicians who have easy access to reliable resistance tests can use these results to guide their decisions. Only the NS5A region, the target of NS5A inhibitors, should be analysed. The test should be based on population sequencing (reporting RASs as "present" or "absent") or deep sequencing with a cut-off of 15% (only RASs that are present in more than 15% of the sequences generated are clinically significant and should be considered). The test should be able to reliably determine the sequence of a region spanning NS5A amino acids 24 to 93. The genotype-specificity of the test should be specified. Table 2 presents RASs that are clinically relevant, i.e. the presence of which may influence decision on the treatment regimen if the resistance test is performed.

Recommendations

- HCV RNA detection and quantification should be made by a sensitive assay with a lower limit of detection of ≤15 IU/ml (**A1**).
- If HCV RNA testing is not available or not affordable, HCV core antigen detection and quantification by EIA can be used as a surrogate marker of HCV replication (**A1**).
- The HCV genotype and genotype 1 subtype (1a or 1b) must be assessed prior to treatment initiation and will determine the choice of therapy, among other parameters (**A1**).
- Systematic testing for HCV resistance prior to treatment is not recommended. Indeed, this obligation would seriously limit access to care and treatment regimens can be optimized without this information (**B1**).
- Physicians who have easy access to a reliable test assessing HCV resistance to NS5A inhibitors (spanning amino acids 24 to 93) can use these results to guide their decisions, as specified in these recommendations. The test should be based on population sequencing (reporting RASs as "present" or "absent") or deep sequencing with a cut-off of 15% (only RASs that are present in more than 15% of the sequences generated must be considered) (**B1**).

Contraindications to therapy

Based on existing knowledge, no absolute contraindications to the direct-acting antivirals (DAAs) approved in the EU region in 2016 exist. Sofosbuvir should be used with caution in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) without other treatment options, as the pharmacokinetics and safety of sofosbuvir-derived metabolites in patients with severe renal dysfunction are still being ascertained. Sofosbuvir is contraindicated in patients receiving amiodarone who cannot switch to another therapy. Treatment regimens comprising an NS3-4A protease inhibitor, such as simeprevir, ritonavir-boosted paritaprevir or grazoprevir, should not be used in patients with Child-Pugh B decompensated cirrhosis or with compensated cirrhosis but with previous episodes of decompensation and are contraindicated in patients with Child-Pugh C decompensated cirrhosis, because of the substantially higher protease inhibitor concentrations in these patients.

Indications for treatment: who should be treated?

To succeed, HCV elimination will require national plans together with forecasted budgeting to expedite unrestricted access to treatment.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, must be considered for therapy.

Treatment must be considered without delay in patients with significant fibrosis (METAVIR score F2 or F3) or cirrhosis (METAVIR score F4), including decompensated cirrhosis; patients with clinically significant extrahepatic manifestations (e.g. symptomatic vasculitis associated with HCV-related mixed cryoglobulinaemia, HCV immune complex-related nephropathy and non-Hodgkin B cell lymphoma); patients with HCV recurrence after liver transplantation; patients at risk of a rapid evolution of liver disease due to concurrent comorbidities (non-liver solid organ or stem cell transplant recipients, diabetes); and individuals at risk of transmitting HCV (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, 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 preventive measures after successful treatment. Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score $\geqslant$18–20 will benefit from transplantation first and antiviral treatment after transplantation, because the probability of significant liver function improvement and delisting is low. However, patients with a MELD score $\geqslant$18–20 with a waiting time before transplantation expected to be more than six months can be treated for their HCV infection.

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 must be considered for therapy (**A1**).
- Treatment should be considered without delay in patients with significant fibrosis or cirrhosis (METAVIR score F2, F3 or F4), including decompensated (Child-Pugh B or C) cirrhosis, in 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), in patients with HCV recurrence after liver transplantation, and in 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) (**A1**).
- Patients with decompensated cirrhosis and an indication for liver transplantation with a MELD score ≥18-20 should be transplanted first and treated after transplantation. If the waiting time is more than 6 months, these patients can be treated before transplantation (**B1**).
- Treatment is not recommended in patients with limited life expectancy due to non-liver-related comorbidities (**B2**).
- National elimination plans require the development of economic partnerships and planning to expedite unrestricted access to treatment (**B1**).

Available drugs in Europe in 2016

The HCV drugs available in Europe are listed in this paragraph and in Table 3. Their known pharmacokinetic profiles and how this impacts drug-drug interactions are presented. For a more comprehensive listing of drug-drug interactions, see Tables 4A to 4F and www.hep-druginteractions.org. For additional information on the disposition of individual DAAs, refer to the Summary of Product Characteristics.

Sofosbuvir

Sofosbuvir should be administered at the dose of 400 mg (one tablet) once per day, with or without food. 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. Renal clearance is the major elimination pathway for GS-331007 with a large part actively secreted. Thus, currently, no sofosbuvir dose recommendation can be given for patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease (ESRD) 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 ($\geqslant$20%) observed in combination with ribavirin were fatigue and headache. The most common adverse events ($\geqslant$20%) observed in combination with pegylated IFN-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-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 known inducers of P-gp, such as rifampin, carbamazepine, phenytoin or St. John's wort. Other potential interactions may occur with rifabutin, rifapentine and modafinil. No significant drug-drug interactions have been reported in studies with the antiretroviral agents emtricitabine, tenofovir, rilpivirine, efavirenz, darunavir/ritonavir and raltegravir, and there are no potential drug-drug interactions with other antiretrovirals.

Sofosbuvir-based regimens are contraindicated in patients who are being treated with the anti-arrhythmic amiodarone due to the risk of life-threatening arrhythmias. Indeed, bradycardia has been observed within hours to days of starting the DAA, but cases have been observed up to 2 weeks after initiating HCV treatment. The mechanism of interaction as well as the role of other co-medications (e.g. β-blockers) is still unclear, although a number of potential mechanisms have been proposed involving P-gp inhibition, protein binding displacement and direct effects of sofosbuvir and/or other DAAs on cardiomyocytes or ion channels. It is most likely to be a combination of these effects. Due to the long half-life of amiodarone, an interaction is possible for several months after discontinuation of amiodarone. If the patient has no cardiac pacemaker *in situ*, it is recommended to wait three months after discontinuing amiodarone before starting a sofosbuvir-based regimen. Sofosbuvir-containing regimens have also been implicated in cardiac toxicity in the absence of amiodarone, but this remains controversial. In the absence of specific drug-drug interaction data, caution should be exercised with antiarrhythmics other than amiodarone.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Table 3. Approved HCV DAAs in Europe in 2016 and ribavirin.

Product	Presentation	Posology
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily (morning)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Sofosbuvir/velpatasvir	Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir	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)
Grazoprevir/elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir	One tablet once daily (morning)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
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 ≥75 kg (or less if dose reduction needed)

Sofosbuvir and ledipasvir

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.

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 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 m^2) or ESRD requiring haemodialysis. Relative to patients with normal renal function (eGFR >80 ml/min/1.73 m^2), the sofosbuvir AUC was 61%, 107% and 171% higher in patients with mild, moderate and severe renal impairment, while the GS-331007 AUC was 55%, 88% and 451% higher, respectively. 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 m^2) or with ESRD.

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 combination. The potential (limited) interactions with sofosbuvir have been previously outlined. Since both ledipasvir and sofosbuvir are transported by intestinal P-gp and breast cancer resistance 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 with sofosbuvir/ledipasvir is contraindicated due to a serious risk of symptomatic or even fatal bradycardia or asystole (see above, mechanism of interaction is unknown). The use of rosuvastatin is also not recommended (thought to be due to inhibition of hepatic organic anion-transporting protein [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 that equivalent to famotidine 40 mg and proton pump inhibitors simultaneously at a dose comparable to omeprazole 20 mg. Real-world data have suggested slightly reduced SVR rates in patients receiving high-dose proton pump inhibitors, reinforcing the need for caution in patients on such drugs who are treated with sofosbuvir and ledipasvir [31].

Sofosbuvir/ledipasvir 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, atazanavir/cobicistat, darunavir/cobicistat, all in combination with tenofovir disoproxil fumarate/emtricitabine) should be used with caution, with frequent renal monitoring if other alternatives are not available. The interaction is not mitigated by staggering administration by 12 h. Tenofovir is also increased in efavirenz-containing regimens and caution is required. The recent approval of tenofovir alafenamide (TAF), giving much reduced plasma tenofovir exposure, means that there is less concern about an interaction leading to increased tenofovir exposure.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

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

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■‡	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■‡	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir; r, ritonavir.

Colour legend

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

Notes:

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

*Known or anticipated increase in tenofovir concentrations in regimens containing tenofovir disoproxil fumarate. Caution and frequent renal monitoring.
‡Atazanavir/cobicistat and darunavir/cobicistat are contraindicated with 3D

Sofosbuvir and velpatasvir

Sofosbuvir and velpatasvir are available in a two-drug fixed-dose combination containing 400 mg of sofosbuvir and 100 mg of velpatasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food.

Velpatasvir is metabolised *in vitro* by CYP2B6, CYP2C8 and CYP3A4. However, due to the slow turnover, the vast majority of drug in plasma is the parent drug. Velpatasvir is transported by P-gp and BCRP and, to a limited extent, by OATP1B1. Biliary excretion of the parent drug is the major route of elimination. The median terminal half-life of velpatasvir following administration of sofosbuvir and velpatasvir is approximately 15 h.

Velpatasvir plasma exposure (AUC) is similar in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function. Cirrhosis (including decompensated cirrhosis) has no clinically relevant effect on velpatasvir exposure in a population pharmacokinetic analysis in HCV infected subjects.

The pharmacokinetics of velpatasvir were studied in HCV-negative patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2). Relative to subjects with normal renal function, velpatasvir AUC was 50% higher and this was not considered to be clinically relevant.

The safety assessment of sofosbuvir and velpatasvir was based on pooled Phase III data. Headache, fatigue and nausea were the most commonly reported adverse events, at a similar frequency to placebo-treated patients.

Due to the disposition profile of velpatasvir, there are some contraindications in relation to co-medications. Drugs that are potent P-gp or potent CYP inducers (e.g., rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, St John's wort) are contraindicated, due to the decrease in sofosbuvir and/or velpatasvir exposure with the potential loss in efficacy. However, there are also drugs that are moderate P-gp or CYP inducers (such as modafinil) which can reduce velpatasvir exposure. Currently this combination would not be recommended with these drugs.

Similar to ledipasvir, there is some concern about the inhibition of P-gp and/or BCRP by velpatasvir, such that there is an increase in exposure of a co-medication that is a substrate for these transporters. The current thinking is that sofosbuvir/velpatasvir may be co-administered with P-gp, BCRP, OATP and CYP inhibitors, but there clearly needs to be some caution with co-medications that have a narrow therapeutic window and in which an increase in drug exposure could potentially have clinical consequences. The colour coding for sofosbuvir/velpatasvir in Tables 4A to 4F reflects this (e.g. for digoxin, dabigatran, ticagrelor, carvedilol, amlodipine, diltiazem, aliskiren).

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

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

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

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

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

● These drugs should not be co-administered.

Notes:

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

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

	SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Atorvastatin	◆	■	■	●	■	■	■
Bezafibrate	◆	◆	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	◆	■	◆	◆	◆
Fenofibrate	◆	■	■	◆	■	◆	◆
Fluvastatin	◆	■	■	■	■	■	◆
Gemfibrozil	◆	◆	◆	●	■	◆	◆
Lovastatin	◆	■	■	●	■	■	■
Pitavastatin	◆	■	■	■	◆	■	■
Pravastatin	◆	■	◆	■	◆	■	■
Rosuvastatin	◆	●	■	■	■	■	■
Simvastatin	◆	■	■	●	■	■	■

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

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

● These drugs should not be co-administered.

Notes:

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

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

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

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 NS5A inhibitor given in a fixed-dose combination with paritaprevir/ritonavir. The recommended dose of this combination is two tablets of ritonavir/paritaprevir/ombitasvir (50 mg/75 mg/12.5 mg per tablet) taken orally once daily with food. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent RNA polymerase in 250 mg tablets administered twice daily in combination with ritonavir/paritaprevir/ombitasvir in genotype 1 patients.

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

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. In Child-Pugh B there is an increase in paritaprevir exposure of 62% with a decrease in ombitasvir of 30%. Thus, no dose adjustment is required for patients with mild hepatic impairment (Child-Pugh A), but the combination of ritonavir-boosted paritaprevir and ombitasvir with or without dasabuvir is not recommended for patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated 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.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

JOURNAL OF HEPATOLOGY

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

		SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Anti-depressants	Amitriptyline	◆	◆	◆	■	◆	◆	◆
	Citalopram	◆	◆	◆	◆	◆	◆	◆
	Duloxetine	◆	◆	◆	◆	◆	◆	◆
	Escitalopram	◆	◆	◆	◆	◆	◆	◆
	Fluoxetine	◆	◆	◆	◆	◆	◆	◆
	Paroxetime	◆	◆	◆	◆	◆	◆	◆
	Sertraline	◆	◆	◆	■	◆	◆	◆
	Trazodone	◆	◆	◆	■	◆	◆	■
	Trimipramine	◆	◆	◆	◆	◆	◆	◆
	Venlafaxine	◆	◆	◆	■	◆	◆	◆
Anti-psychotics	Amisulpiride	◆	◆	◆	◆	◆	◆	◆
	Aripiprazole	◆	◆	◆	■	■	◆	■
	Chlorpromazine	◆	◆	◆	■	◆	◆	◆
	Clozapine	◆	◆	◆	■	◆	◆	■
	Flupentixol	◆	◆	◆	■	◆	◆	◆
	Haloperidol	◆	◆	◆	■	◆	◆	■
	Olanzapine	◆	◆	◆	■	◆	◆	◆
	Paliperidone	◆	■	◆	■	◆	■	■
	Quetiapine	◆	◆	◆	●	■	◆	■
	Risperidone	◆	◆	◆	■	◆	◆	■
	Zuclopentixol	◆	◆	◆	■	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

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

● These drugs should not be co-administered.

Notes:

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

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

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

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

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

● These drugs should not be co-administered.

Notes:

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

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 contraindicated 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 contraindicated are enzyme inducers that might compromise virological efficacy, e.g. carbamazepine,

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

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

	SOF	SOF/ LDV	SOF/ VEL	3D	GZR/ EBR	DCV	SIM
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	◆	●
Etanercept	◆	◆	◆	◆	■	◆	◆
Everolimus	◆	■	■	●	■	■	■
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	◆	■
Tacrolimus	◆	◆	◆	■	■	◆	■

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir.

Colour legend

◆ No clinically significant interaction expected.

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

● These drugs should not be co-administered.

Notes:

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

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 contraindications, 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 contraindicated. Efavirenz, etravirine and nevirapine are contraindicated, 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. Cobicistat-containing regimens should not be used because of the additional boosting effect.

Grazoprevir and elbasvir

Grazoprevir and elbasvir are available in a two-drug fixed-dose combination containing 100 mg of grazoprevir and 50 mg of elbasvir in a single tablet. The recommended dose of the combination is one tablet taken orally once daily with or without food.

Grazoprevir and elbasvir are partially metabolised by CYP3A4, but no circulating metabolites are detected in plasma. The principal route of elimination is biliary and faecal with <1% recovered in urine. Grazoprevir is transported by P-gp and OATP1B1, while elbasvir is a substrate for P-gp. Both elbasvir (>99.9%) and grazoprevir (98.8%) are extensively bound to plasma proteins. The terminal half-life values are approximately 24 and 31 h, respectively.

Pharmacokinetic data from hepatic impairment studies in non-HCV infected subjects have demonstrated a decrease in elbasvir AUC in Child-Pugh A (40%), Child-Pugh B (28%) and Child-Pugh C (12%). In contrast, grazoprevir exposure is increased in Child-Pugh A (70%), Child-Pugh B (5-fold) and Child-Pugh C (12-fold). Based on these data, there is a contraindication for elbasvir/grazoprevir in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

No dose adjustment is required in patients with mild, moderate of severe renal impairment (including patients on haemodialysis or peritoneal dialysis). There is an increase in elbasvir (65%) and grazoprevir (86%) exposure in non-HCV infected subjects with an eGFR <30 ml/min/1.73 m^2, but this is not considered to be clinically significant.

The safety of elbasvir/grazoprevir is based on Phase II and III clinical studies with the most commonly reported adverse reactions being fatigue and headache. Rare cases (0.8%) of substantial ALT level elevations were reported, slightly more frequently in female, Asian and elderly patients. Less than 1% of subjects treated with elbasvir/grazoprevir with or without ribavirin discontinued treatment due to adverse events.

Since elbasvir and grazoprevir are substrates of CYP3A and P-gp, inducers of these proteins such as efavirenz, etravirine, phenytoin, carbamazepine, bosentan, modafinil and St John's wort may cause a marked decrease in plasma exposure of both DAAs and are therefore contraindicated. Strong inhibitors of CYP3A (e.g. boosted protease inhibitors, azole antifungals), which may markedly increase plasma concentrations, are either contraindicated or not recommended. In addition to inhibition of CYP3A, grazoprevir plasma concentrations may also be markedly increased by inhibitors of OATP1B1 (including boosted protease inhibitors, cobicistat, cyclosporin, single dose rifampicin). However, there is no effect of acid-reducing agents on the absorption of either DAA.

The potential for grazoprevir/elbasvir to affect other medications is relatively low, although grazoprevir is a weak CYP3A inhibitor (approximately 30% increase in midazolam exposure) and elbasvir a weak inhibitor of P-gp. There needs to be some caution when co-administering drugs that use CYP3A and P-gp in their disposition (e.g. tacrolimus, some statins, dabigatran, ticagrelor).

Based on the findings above, there are limitations on which antiretrovirals can be co-administered with elbasvir/grazoprevir. Currently the antiretrovirals that can be used are the nucleotide reverse transcriptase inhibitors abacavir, lamivudine, tenofovir (either as tenofovir disoproxil fumarate or as tenofovir alafenamide), emtricitabine, rilpivirine, raltegravir, dolutegravir and maraviroc (Table 4A).

Daclatasvir

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 with or without food. 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

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

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 CYP34A 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 contraindicated. 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, darunavir/cobicistat 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 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.

Simeprevir

Simeprevir should be administered at the dose of 150 mg (one capsule) once per day with food. 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) and 5.2-fold higher in HCV uninfected subjects with severe hepatic impairment (Child-Pugh C). No dose adjustment is required in patients with mild (Child-Pugh A) hepatic impairment, but simeprevir is not recommended in patients with moderate (Child-Pugh B) hepatic impairment and contraindicated in those with severe (Child-Pugh C) hepatic impairment.

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 ESRD, 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 pegylated IFN-α and ribavirin were rash (including photosensitivity), pruritus and nausea. Because simeprevir is an inhibitor of the hepatic transporters OATP1B1 and MRP2 [32], 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 contraindicated 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.

Ribavirin

The ribavirin dose should be 1000 or 1200 mg/day, based on body weight (<75 kg or $\geqslant$75 kg, respectively), split in two administrations.

The main side effects associated with the administration of ribavirin are rash, cough, and haemolytic anaemia, which can be managed by stepwise dose reductions. Ribavirin has a low potential for drug-drug interactions, and dose adjustment is needed in patients with severe renal insufficiency or ESRD who need ribavirin.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Recommendations

- Numerous and complex drug-drug interactions are possible with the HCV DAAs. Therefore, the potential for drug-drug interactions should be considered in all patients undergoing treatment with DAAs. This requires a thorough drug-drug interaction risk assessment prior to starting therapy and before starting other medications during treatment (**A1**).
- The prescribing information for each DAA contains important information on drug-drug interactions. Summary data on key interactions can be found in Tables 4A-4F in this document. A key Internet resource is www.hep-druginteractions.org where recommendations are regularly updated (**A1**).
- Drug-drug interactions are a key consideration in treating HIV-HCV co-infected patients and it is vital that close attention is paid to anti-HIV drugs that are contraindicated, not recommended or require dose adjustment with particular DAA regimens (**A1**).
- Patients should be educated on the importance of adherence to therapy, following the dosing recommendations and reporting the use of over-the-counter medications, medications bought via the internet, and use of party or recreational drugs (**B1**).

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

In 2016 and onwards, IFN-free regimens are the best options in treatment-naïve and treatment-experienced, DAA-naïve patients with compensated and decompensated liver disease, because of their virological efficacy, ease of use and tolerability. Indications depend on the HCV genotype/subtype, the severity of liver disease, and/or the results of prior therapy. 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 and Table 4A).

The panel recognises the heterogeneity of per capita incomes and health insurance systems across Europe and in other regions, and therefore the imposition to continue to utilise regimens with pegylated IFN-α and ribavirin, with or without DAAs, such as telaprevir, boceprevir, simeprevir or sofosbuvir. However, the advent of new DAAs implies that these regimens are not recommended in 2016. 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.

Recommendations

- Indications for HCV treatment in HCV/HIV coinfected persons are identical to those in patients with HCV monoinfection (**A1**).
- IFN-free regimens are the best options in HCV-monoinfected and in HIV-coinfected patients without cirrhosis or with compensated (Child-Pugh A) 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. Treatment alterations or dose adjustments may be needed in case of interactions with antiretroviral drugs (**A1**).

Table 5 shows the IFN-free combination regimens that represent valuable options for each genotype. 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 6 and 7 for patients without cirrhosis and with compensated (Child-Pugh A) cirrhosis, respectively.

These options are considered equivalent for a given genotype, and their order of presentation does not indicate any superiority of preference, unless specified so. By convention, the combination regimens listed start with fixed-dose, single-pill combinations (sofosbuvir-based followed by sofosbuvir-free), followed by combinations of sofosbuvir with another drug in a different pill.

Treatment of HCV genotype 1 infection

Five treatment options are available in 2016 for patients infected with HCV genotype 1 (Table 5). The combination of sofosbuvir and simeprevir was shown to yield lower SVR12 rates than other combinations of DAAs in real-world studies and is therefore not recommended as an option equivalent to the others [33–36]. However, in areas where it is the only available IFN-free option, the combination of sofosbuvir and simeprevir with or without ribavirin can be used to treat genotype 1 infection, according to prior recommendations [37].

In settings where none of the proposed IFN-free options is available, the double combination of pegylated IFN-α and ribavirin, or the triple combination of pegylated IFN-α, ribavirin and telaprevir, boceprevir, simeprevir or sofosbuvir remain acceptable for patients likely to respond to these regimens until new DAAs become available and affordable; see prior EASL Clinical Practice Guidelines [37–39].

Table 5. IFN-free combination treatment regimens available as valuable options for each HCV genotype.

Combination regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Sofosbuvir + ribavirin	No	Suboptimal	Suboptimal	No	No
Sofosbuvir/ledipasvir ± ribavirin	Yes	No	No	Yes	Yes
Sofosbuvir/velpatasvir ± ribavirin	Yes	Yes	Yes	Yes	Yes
Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin	Yes	No	No	No	No
Ombitasvir/paritaprevir/ritonavir ± ribavirin	No	No	No	Yes	No
Grazoprevir/elbasvir ± ribavirin	Yes	No	No	Yes	No
Sofosbuvir + daclatasvir ± ribavirin	Yes	Yes	Yes	Yes	Yes
Sofosbuvir + simeprevir ± ribavirin	Suboptimal	No	No	Yes	No

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Genotype 1, Option 1: Sofosbuvir/ledipasvir

- Patients infected with HCV genotype 1 can be treated with the fixed dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**A1**).
- Treatment can 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 in patients with F3 fibrosis (**B1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1b with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**A1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).
- If reliable NS5A resistance testing is performed, treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis who have NS5A RASs that confer high-level resistance to ledipasvir (M28A/G/T, Q30E/G/H/K/R, L31M/V, P32L/S, H58D, and/or Y93C/H/N/S) detected at baseline should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with ribavirin, whereas those without ledipasvir RASs at baseline can be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**B1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1a 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**).

Comments: This recommendation is based on the results of the four Phase III trials ION-1, ION-2, ION-3 and ION-4 [40–43] and several post-hoc analyses of pooled data from Phase II and III clinical trials.

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 [40].

In ION-3 in treatment-naïve patients without cirrhosis (F3 fibrosis was present 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. Post-hoc analysis indicated that 8 weeks of treatment yielded an SVR12 rate of 97% (119/123) in patients with an HCV RNA level <6 million (6.8 Log) IU/ml at baseline [42,44]. These results were confirmed by real-world studies from Europe and the United States in the same subgroup of patients, showing comparably high SVR12 rates: 95% (251/263) in the TRIO cohort, 97% (150/154) in the HCV TARGET cohort, 97% (155/159) in the GECCO cohort, 99% (127/128) in the IFI cohort, and 98% (47/48) in the VA-Ohio cohort [44]. Because HCV RNA level determination and non-invasive fibrosis scoring can be inaccurate within this range of values with currently available HCV RNA assays, there is uncertainty whether patients with F3 fibrosis and an HCV RNA level <6 million (6.8 Log) IU/ml at baseline should be treated for 8 or 12 weeks [45].

In ION-2, in treatment-experienced patients (previously treated with pegylated IFN-α and ribavirin or pegylated IFN-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 [46].

In ION-4, an open-label study in patients coinfected with HIV receiving an antiretroviral regimen of tenofovir and emtricitabine with efavirenz, rilpivirine or raltegravir (20% with cirrhosis, 45% treatment-naïve, 55% treatment-experienced of whom 36% had received a previous HCV DAA), the SVR12 rate was 96% (314/327), and was identical in patients infected with genotype 1a and 1b [43].

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 [47]. 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 $<75 \times 10^3/\mu l$ was associated with a lower rate of SVR among treatment-experienced patients (based on 28 patients) [47]. 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 (Child-Pugh A) cirrhosis who failed to achieve an SVR after treatment with pegylated IFN-α, ribavirin and either telaprevir or boceprevir yielded SVR12 rates of 96% (74/77) and 97% (75/77), respectively [48].

A pooled data analysis of 1566 patients who received the current EASL or AASLD/IDSA guidelines-recommended sofosbuvir plus ledipasvir regimens in Phase II and III clinical trials showed that the presence of NS5A RASs at baseline had no impact on SVR12 in treatment-naïve patients, regardless of the presence of cirrhosis. Indeed, SVR12 was achieved in 99% (187/189) and 99% (504/509) of treatment-naïve non-cirrhotic patients with and without NS5A class RASs at baseline, respectively, and in 96% (26/27) and 96% (65/68) of treatment-naïve cirrhotic patients with and without NS5A class RASs at baseline, respectively [49]. However, the presence of RASs conferring high-level ledipasvir resistance at baseline (>100-fold increase in EC50 in the replicon system: M28A/G/T, Q30E/G/H/K/R, L31M/V, P32L/S, H58D, and/or Y93C/H/N/S) was associated with a lower rate of SVR12 in treatment-experienced patients without cirrhosis treated for 12 weeks without ribavirin: 90% (79/88) *vs.* 99% (298/300) in patients with and without NS5A class RASs at baseline, respectively [49]). Another pooled data analysis of Phase II and III clinical trials with sofosbuvir and ledipasvir showed that the presence of RASs conferring high-level ledipasvir resistance at treatment baseline had an effect on SVR12 in patients infected

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Table 6. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on pegylated IFN-α and ribavirin (treatment-experienced, DAA-naïve patients).

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 1a	Treatment-naïve	8-12 wk, no ribavirin	12 wk, no ribavirin	12 wk with ribavirin	No	12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml[b]	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin[a] or 24 wk, no ribavirin					12 wk with ribavirin[a] or 24 wk, no ribavirin	
Genotype 1b	Treatment-naïve	8-12 wk, no ribavirin	12 wk, no ribavirin	8-12 wk, no ribavirin	No	12 wk, no ribavirin	12 wk, no ribavirin	No
	Treatment-experienced	12 wk, no ribavirin		12 wk, no ribavirin				
Genotype 2	Both	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
Genotype 3	Treatment-naïve	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced		12 wk with ribavirin[c] or 24 wk, no ribavirin				12 wk with ribavirin[c] or 24 wk, no ribavirin	
Genotype 4	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk with ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin				12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml	12 wk with ribavirin or 24 wk, no ribavirin	12 wk with ribavirin or 24 wk, no ribavirin
Genotype 5 or 6	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin					12 wk with ribavirin or 24 wk, no ribavirin	

[a]Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available.
[b]Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available.
[c]Add ribavirin only in patients with NS5A RAS Y93H at baseline if RAS testing available.

with HCV genotype 1a, but not in those infected with genotype 1b [49,50]. The addition of ribavirin prevented the effect of pre-existing NS5A RASs on SVR12: SVR rates of 88% (23/26) without ribavirin *vs.* 94% (32/34) with ribavirin were observed in cirrhotic patients with NS5A RASs treated for 12 weeks; SVR rates of 85% (17/20) *vs.* 100% (14/14) were observed in those treated for 24 weeks without and with ribavirin, respectively [50].

SVR12 rates in the same order as in the clinical trials were observed in real-world studies from various continents.

Genotype 1, Option 2: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 1 can be treated with the fixed dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Table 7. Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis, including treatment-naïve patients and patients who failed on a treatment based on pegylated IFN-α and ribavirin (treatment-experienced, DAA-naïve patients).

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 1a	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	24 wk with ribavirin	No	12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml[b]	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin[a] or 24 wk, no ribavirin					12 wk with ribavirin[a] or 24 wk, no ribavirin	
Genotype 1b	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk, no ribavirin	12 wk, no ribavirin	No
	Treatment-experienced							
Genotype 2	Both	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
Genotype 3	Treatment-naïve	No	12 wk with ribavirin[c] or 24 wk, no ribavirin	No	No	No	24 wk with ribavirin	No
	Treatment-experienced							
Genotype 4	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk with ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin				12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml	12 wk with ribavirin or 24 wk, no ribavirin	12 wk with ribavirin or 24 wk, no ribavirin
Genotype 5 or 6	Treatment-naïve	12 wk, no ribavirin	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin					12 wk with ribavirin or 24 wk, no ribavirin	

[a]Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available.
[b]Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available.
[c]Add ribavirin only in patients with NS5A RAS Y93H at baseline if RAS testing available.

Comments: This recommendation is based on the results of the Phase III ASTRAL-1 trial in patients with HCV genotype 1 infection (22% with cirrhosis, 66% treatment-naïve, 34% treatment-experienced, 44% of whom were exposed to previous DAA) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. An SVR12 was observed in 98% (323/328) of patients, including 98% (206/210) in those infected with genotype 1a and 99% (117/118) in those infected with genotype 1b [51].

In the ASTRAL-5 trial in HIV coinfected patients, the SVR12 rates with the same regimen were 95% (62/65) and 92% (11/12) in treatment-naïve or experienced patients with or without cirrhosis infected with genotype 1a or 1b, respectively [52].

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Genotype 1, Option 3: Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

- Patients infected with HCV genotype 1 can 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), and dasabuvir (250 mg) (one tablet twice daily) (**A1**).
- Patients infected with subtype 1b with or without compensated cirrhosis should receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 12 weeks without ribavirin (**A1**).
- Treatment-naïve patients infected with subtype 1b without cirrhosis can receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 8 weeks without ribavirin, with caution in patients with F3 fibrosis (**B1**).
- Patients infected with subtype 1a without cirrhosis should receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir 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 compensated cirrhosis should receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir 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 10 Phase III trials. In SAPPHIRE-1 in treatment-naïve patients without cirrhosis treated with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir with ribavirin for 12 weeks, the SVR12 rates were 95% (307/322) in subtype 1a and 98% (148/151) in subtype 1b patients [53]. In PEARL-4, 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-3, 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 [54]. In MALACHITE-1, the SVR12 rates in treatment-naïve non-cirrhotic patients were 97% (67/69) with ribavirin for 12 weeks in those infected with genotype 1a, and 98% (81/83) without ribavirin for 12 weeks in those infected with genotype 1b [55]. In the TURQUOISE-1 study in treatment-naïve, non-cirrhotic patients coinfected 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 [56]. In the GARNET study, the SVR12 rate was 97% (161/166) in patients with genotype 1b infection and no cirrhosis (METAVIR score F0 to F3) after 8 weeks of treatment with ombitasvir, paritaprevir and ritonavir plus dasabuvir without ribavirin. Among the 15 patients with F3 fibrosis included in this study, 13 achieved SVR12 (data provided to the panel by Abbvie, on request).

In non-cirrhotic treatment-experienced patients (pegylated IFN-α and ribavirin failures) treated with this combination with ribavirin for 12 weeks in SAPPHIRE-2, 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 [57]. 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-2 trial [58]. In the MALACHITE-2 trial, in treatment-experienced non-cirrhotic patients infected with genotype 1a (19%) or 1b (81%) receiving this combination with ribavirin for 12 weeks, the SVR12 rate was 99% (100/101) [55].

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-2 trial. SVR12 was achieved in 92% (239/261) of genotype 1a and 99% (118/119) of genotype 1b patients [59]. In patients with α-fetoprotein level <20 ng/ml, platelet count $\geqslant 90 \times 10^9$/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 [59]. In treatment-naïve and treatment-experienced patients with compensated cirrhosis infected with genotype 1b, the rate of SVR was 100% (60/60) after 12 weeks without ribavirin in the TURQUOISE-3 trial [60].

SVR12 rates in the same order as in the clinical trials were observed in a large number of real-world studies from various continents.

Genotype 1, Option 4: Grazoprevir/elbasvir

- Patients infected with HCV genotype 1 can be treated with the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients infected with subtype 1b with or without compensated cirrhosis should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**A1**).
- If no NS5A resistance testing is performed, treatment-naïve and treatment-experienced patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level >800,000 IU/ml (5.9 $\log_{10}$ IU/ml) at baseline should receive the combination of grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 $\log_{10}$ IU/ml) at baseline should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).
- If reliable NS5A resistance testing is performed, treatment-naïve and treatment-experienced patients infected with subtype 1a with or without compensated cirrhosis should receive the combination of grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) if their HCV RNA level is >800,000 IU/ml and NS5A RASs that confer resistance to elbasvir (M28A/G/T, Q30D/E/G/H/K/L/R, L31F/M/V, H58D and/or Y93C/H/N/S) are present at baseline. Patients infected with subtype 1a with or without compensated cirrhosis with an HCV RNA level ≤800,000 IU/ml and those with an HCV RNA level >800,000 IU/ml without elbasvir NS5A RASs at baseline should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).

Comments: This recommendation is based on the results of three Phase III trials and subsequent post-hoc analyses of pooled Phase II and III clinical trial data.

In the C-EDGE-TN trial, in treatment-naïve patients infected with genotype 1a or 1b receiving grazoprevir and elbasvir for 12 weeks without ribavirin, the SVR12 rates were 92% (144/157) in patients infected with genotype 1a and 99% (129/131) in those infected with genotype 1b. The presence of compensated cirrhosis in 23% of patients had no effect on SVR12. In the open-label C-EDGE-COINFECTION trial, treatment-naïve patients coinfected with HIV with or without compensated cirrhosis were treated with grazoprevir and elbasvir for 12 weeks. The SVR12 rates were 97% (139/144) in genotype 1a- and 95% (42/44) in

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

genotype 1b-infected patients [61]. When considering the HCV RNA level and the presence at baseline of RASs conferring elbasvir resistance (>5-fold elbasvir loss of potency *in vitro*, including M28A/G/T, Q30D/E/G/H/K/L/R, L31F/M/V, H58D and/or Y93C/H/N/S) in a pooled efficacy population of patients with genotype 1a infection who were treatment-naïve from Phase II and III trials treated without ribavirin for 12 weeks, the SVR12 rates were: 99% (118/119) in patients with an HCV RNA level ⩽800,000 IU/ml without elbasvir RASs; 100% (3/3) in patients with an HCV RNA level ⩽800,000 IU/ml with elbasvir RASs; 97% (265/273) in patients with an HCV RNA level >800,000 IU/ml without elbasvir NS5A RASs; and 52% (11/21) in patients with an HCV RNA level >800,000 IU/ml with elbasvir NS5A RASs present at baseline (data provided to the panel by Merck, on request) [62].

In treatment-experienced patients included in the C-EDGE-TE Phase III trial, including 34% of patients with compensated cirrhosis, the SVR12 rates in genotype 1a and 1b patients, respectively, were: 92% (55/60) and 100% (34/34) after 12 weeks of grazoprevir/elbasvir without ribavirin; 93% (56/60) and 97% (28/29) after 12 weeks with ribavirin; 94% (45/48) and 98% (46/47) after 16 weeks without ribavirin; and 100% (55/55) and 100% (37/37) after 16 weeks with ribavirin [63]. In a pooled efficacy population of treatment-experienced patients with genotype 1a from Phase II and III trials treated without ribavirin for 12 weeks, the SVR12 rates were: 100% (14/14) in patients with an HCV RNA level ⩽800,000 IU/ml without elbasvir RASs; 97% (67/69) in patients with an HCV RNA level >800,000 IU/ml without elbasvir NS5A RASs; and 29% (2/7) in patients with an HCV RNA level >800,000 IU/ml with elbasvir NS5A RASs present at baseline (no patients with an HCV RNA level ⩽800,000 IU/ml had elbasvir RASs) (data provided to the panel by Merck, on request).

Genotype 1, Option 5: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 1 can be treated with a combination of sofosbuvir (400 mg) in one tablet and daclatasvir (60 mg) in another tablet administered once daily (**A1**).
- The dose of daclatasvir must be adjusted to 30 mg in HIV-coinfected patients receiving ritonavir- or cobicistat-boosted atazanavir or cobicistat-boosted elvitegravir, and to 90 mg in HIV-coinfected patients receiving efavirenz (**B1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**A1**).
- Treatment-experienced, DAA-naïve patients infected with genotype 1b with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**A1**).
- Based on data with the equivalent sofosbuvir and ledipasvir combination, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) is recommended in treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis receiving the combination of sofosbuvir and daclatasvir for 12 weeks (**C2**).
- If reliable NS5A resistance testing is performed, treatment-experienced, DAA-naïve patients infected with genotype 1a with or without compensated cirrhosis with NS5A class RASs detected at baseline should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with ribavirin, whereas those without NS5A class RASs at baseline can be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**C2**).
- Treatment-experienced, DAA-naïve patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (**B1**).

Comments: Phase IIb results have been published with the combination of sofosbuvir and daclatasvir in patients without cirrhosis [64]. 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 pegylated IFN-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) [64].

In the ALLY-2 study, HIV-HCV coinfected patients were treated with sofosbuvir and daclatasvir without ribavirin for 12 weeks. The dose of daclatasvir was adjusted to 30 mg in patients receiving ritonavir-boosted HIV protease inhibitors. The SVR12 rates were 96% (100/104) in genotype 1a- and 100% (23/23) in genotype 1b-infected patients, similarly high in treatment-naïve and treatment-experienced patients (overall 97% [96/99] and 98% [51/52], respectively) [65]. In the ALLY-1 study, 91% (10/11) of patients with compensated cirrhosis achieved SVR12 [66].

Treatment of HCV genotype 2 infection

Two first-line treatment options are available for patients infected with HCV genotype 2, including the fixed-dose combination of sofosbuvir and velpatasvir and the combination of sofosbuvir and daclatasvir (Table 5). The combination of sofosbuvir and ribavirin was found to be suboptimal in clinical trials and real-world studies. In settings where these options are not available, the combination of pegylated IFN-α and ribavirin or the combination of sofosbuvir and ribavirin remain acceptable, according to previously published EASL Clinical Practice Guidelines [38].

Genotype 2, Option 1: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 2 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Comments: This recommendation is based on the results of the Phase III ASTRAL-2 trial in patients with HCV genotype 2 infection (14% with compensated cirrhosis, 86% treatment-naïve, 14% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, showing SVR12 in 99% (133/134) of patients [67]. In the ASTRAL-5 trial in HIV coinfected patients, the SVR12 rate with the same regimen was 100% (11/11) [52].

Genotype 2, Option 2: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 2 can be treated with a combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**B1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Comments: Daclatasvir is active *in vitro* against HCV genotype 2. Thus, although few data are available with this genotype, and by analogy with the results obtained with the combination of sofosbuvir and velpatasvir, the combination of sofosbuvir and daclatasvir appears as a reasonable option for patients with genotype 2 infection.

Treatment of HCV genotype 3 infection

In patients infected with HCV genotype 3, the combination of sofosbuvir and ribavirin is suboptimal and should not be used. The fixed-dose combination of sofosbuvir and velpatasvir or the combination of sofosbuvir and daclatasvir, with or without ribavirin, are the most efficacious options for patients infected with HCV genotype 3 (Table 5). In settings where none of these options is available, the double combination of pegylated IFN-α and ribavirin, the double combination of sofosbuvir and ribavirin and the triple combination of pegylated IFN-α, ribavirin and sofosbuvir remain acceptable, according to previous EASL Clinical Practice Guidelines [38]. Because ledipasvir is considerably less potent against genotype 3 than velpatasvir or daclatasvir, the combination of sofosbuvir plus ledipasvir is not recommended in patients infected with HCV genotype 3.

Genotype 3, Option 1: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 3 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily, with or without ribavirin (**A1**).
- Treatment-naïve patients without cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).
- If no NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**A1**).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis, as well as treatment-naïve and treatment-experienced patients with compensated cirrhosis, with the NS5A RAS Y93H detectable at baseline should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RAS Y93H at baseline should receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).
- NS5A resistance testing for HCV genotype 3 may be technically challenging, so that a reliable result is not guaranteed in all cases (**B2**).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and velpatasvir for 24 weeks without ribavirin (**C1**).

Comments: This recommendation is based on the results of the Phase III ASTRAL-3 trial in patients with HCV genotype 3 infection (29% with compensated cirrhosis, 74% treatment-naïve, 26% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin. The SVR12 rates were 98% (160/163) in treatment-naïve patients without cirrhosis, 93% (40/43) in treatment-naïve patients with compensated cirrhosis, 91% (31/34) in treatment-experienced patients without cirrhosis and 89% (33/37) in treatment-experienced patients with compensated cirrhosis [67]. In ASTRAL-3, the SVR12 rate was 97% (225/231) in patients without NS5A RASs at baseline, *vs.* 88% (38/43) in those with detectable NS5A RASs at baseline (present in 16% of cases) [67]. In the ASTRAL-5 trial in HIV coinfected patients, the SVR12 rate with the same regimen was 92% (11/12) [52].

Genotype 3, Option 2: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 3 can be treated with a combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**A1**).
- Treatment-naïve patients infected with HCV genotype 3 without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).
- If no NS5A resistance testing is performed, treatment-experienced patients infected with HCV genotype 3 without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- If reliable NS5A resistance testing is performed, treatment-experienced patients without cirrhosis with the NS5A RAS Y93H detectable at baseline should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). Patients without the NS5A RASs Y93H at baseline should receive the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B1**).
- Treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**C1**).
- Patients with contraindications to the use of ribavirin or with poor tolerance to ribavirin on treatment should receive the combination of sofosbuvir and daclatasvir for 24 weeks without ribavirin (**C1**).

Comments: In a Phase IIb trial with this combination for 24 weeks [64], 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 [68].

In the ALLY-3+ trial, the SVR12 rates in patients with advanced fibrosis (METAVIR score F3) were 100% (6/6) after 12 weeks of sofosbuvir and daclatasvir with ribavirin, and 100% (8/8) after 16 weeks of the same regimen. In patients with cirrhosis, the SVR12 rates were 83% (15/18) after 12 weeks of sofosbuvir and daclatasvir with ribavirin, and 89% (16/18) after 16 weeks of the same regimen. The SVR12 rates were 88% (14/16) and 86% (12/14), respectively, in treatment-experienced cirrhotic patients [69]. No clinical trial data with 24 weeks of sofosbuvir and daclatasvir with ribavirin are available in cirrhotic patients.

Treatment of HCV genotype 4 infection

Six treatment options are available in 2016 for patients infected with HCV genotype 4 (Table 5). In settings where none of the proposed options is available, the double combination of pegylated IFN-α and ribavirin, or the triple combination of pegylated IFN-α, ribavirin and simeprevir, or the triple combination of pegylated IFN-α, ribavirin and sofosbuvir remain acceptable for

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

selected patients likely to respond to these regimens until new DAAs become available and affordable; see prior EASL Clinical Practice Guidelines [37–39].

Genotype 4, Option 1: Sofosbuvir/ledipasvir

- Patients infected with HCV genotype 4 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**A1**).
- Treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- Treatment-experienced patients with or without 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**).

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) [70]. In another Phase II trial, patients were treated with the combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin. The SVR12 rates were 96% (21/22) in treatment-naïve and 91% (20/22) in treatment-experienced individuals; the split was 91% (31/34) in patients without cirrhosis and 100% (10/10) in those with cirrhosis [71].

Genotype 4, Option 2: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 4 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Comments: This recommendation is based on the results of the Phase III ASTRAL-1 trial in patients with HCV genotype 4 infection (23% with cirrhosis, 55% treatment-naïve, 45% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, showing SVR12 in 100% (116/116) of patients [51]. In the ASTRAL-5 trial in HIV coinfected patients receiving the same treatment regimen, the SVR12 rate was 100% (4/4) [52].

Genotype 4, Option 3: Ombitasvir/paritaprevir/ritonavir

- Patients infected with HCV genotype 4 can 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), without dasabuvir (**A1**).
- Patients infected with HCV genotype 4 with and without compensated cirrhosis should be treated with the fixed-dose combination of ombitasvir, paritaprevir and ritonavir for 12 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 the PEARL-1 and AGATE-1 trials. In PEARL-1, treatment-naïve and treatment-experienced non-cirrhotic patients infected with genotype 4 treated for 12 weeks with the combination of ombitasvir and ritonavir-boosted paritaprevir with ribavirin achieved SVR12 in 100% (42/42) and 100% (49/49) of cases, respectively [72]. In AGATE-1, which included 51% of treatment-naïve and 49% of treatment-experienced patients with compensated cirrhosis, 12 weeks of ombitasvir and ritonavir-boosted paritaprevir with ribavirin yielded a 97% (57/59) SVR12 rate [73].

Genotype 4, Option 4: Grazoprevir/elbasvir

- Patients infected with HCV genotype 4 can be treated with the fixed-dose combination of grazoprevir (100 mg) and elbasvir (50 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients infected with genotype 4 with or without compensated cirrhosis should receive the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**A1**).
- By analogy to genotype 1a patients, treatment-experienced patients infected with genotype 4 with or without compensated cirrhosis with an HCV RNA level at baseline >800,000 IU/ml should receive the combination of grazoprevir and elbasvir for 16 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B2**).

Comments: This recommendation is based on the results of three Phase III trials including a small number of patients infected with genotype 4. In the C-EDGE-TN trial, the SVR12 rate was 100% (18/18) in treatment-naïve patients infected with genotype 4 receiving grazoprevir and elbasvir for 12 weeks without ribavirin (including 12% with cirrhosis) [74]. In the open-label C-EDGE-COINFECTION trial, treatment-naïve patients with HCV genotype 4 coinfected with HIV with or without compensated cirrhosis were treated with grazoprevir and elbasvir for 12 weeks. The SVR12 rate was 96% (27/28) [61]. In treatment-experienced patients included in the C-EDGE-TE Phase III trial, including 46% with cirrhosis, the SVR12 rates were: 87% (7/8) after 12 weeks of grazoprevir and elbasvir without ribavirin; 93% (14/15) after 12 weeks of grazoprevir and elbasvir with ribavirin; 60% (3/5) after 16 weeks of grazoprevir and elbasvir without ribavirin; and 100% (8/8) after 16 weeks of grazoprevir and elbasvir with ribavirin [63]. The small number of patients did not allow for assessing the influence of the HCV RNA level and of the presence of elbasvir-specific RASs at baseline on the SVR12.

Genotype 4, Option 5: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 4 can be treated with the combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**B2**).
- Treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B2**).
- Based on data with other combinations, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B2**).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B2**).

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Comments: There is little data with this combination in patients infected with HCV genotype 4 (four patients in the ALLY-1 trial and three patients in the ALLY-2 trial who all achieved SVR). 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.

Genotype 4, Option 6: Sofosbuvir and simeprevir

- Patients infected with HCV genotype 4 can be treated with the combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) (**A1**).
- Treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and simeprevir for 12 weeks without ribavirin (**A1**).
- Based on data with other combinations, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and simeprevir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**C1**).

Comments: This recommendation is based on the results of the PLUTO open-label Phase III clinical trial in 40 patients infected with genotype 4, including 18% with cirrhosis, 32% who were treatment-naïve and 68% who were treatment-experienced, showing SVR12 in 100% of patients [75].

Treatment of HCV genotype 5 or 6 infection

The three treatment options for patients infected with HCV genotypes 5 or 6 are the fixed-dose combinations of sofosbuvir and ledipasvir, the fixed-dose combination of sofosbuvir and velpatasvir, and the combination of sofosbuvir and daclatasvir. In settings where none of these options is available, the combination of pegylated IFN-α and ribavirin or the triple combination of pegylated IFN-α, ribavirin and sofosbuvir remain acceptable [37,38].

Genotype 5 or 6, Option 1: Sofosbuvir/ledipasvir

- Patients infected with HCV genotype 5 or 6 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks without ribavirin (**B1**).
- Based on data in patients infected with HCV genotype 1, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and ledipasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B1**).
- Treatment-experienced patients with or without 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**).

Comments: In a Phase II trial, 41 treatment-naïve and treatment-experienced patients infected with HCV genotype 5, including 9 with compensated cirrhosis, were treated with sofosbuvir and ledipasvir without ribavirin for 12 weeks: 95% (39/41) achieved SVR12 [76]. The combination of sofosbuvir and ledipasvir, administered for 12 weeks without ribavirin in treatment-naïve and treatment-experienced patients infected with genotype 6 yielded an SVR rate of 96% (24/25) [77].

Genotype 5 or 6, Option 2: Sofosbuvir/velpatasvir

- Patients infected with HCV genotype 5 or 6 can be treated with the fixed-dose combination of sofosbuvir (400 mg) and velpatasvir (100 mg) in a single tablet administered once daily (**A1**).
- Treatment-naïve and treatment-experienced patients with or without compensated cirrhosis should be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin (**A1**).

Comments: This recommendation is based on the results of the Phase III ASTRAL-1 trial in patients with HCV genotype 5 (14% with cirrhosis, 69% treatment-naïve, 31% treatment-experienced) or genotype 6 (15% with cirrhosis, 93% treatment-naïve, 17% treatment-experienced) treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, showing SVR12 in 97% (34/35) and 100% (41/41) of them, respectively [51].

Genotype 5 or 6, Option 3: Sofosbuvir and daclatasvir

- Patients infected with HCV genotype 5 or 6 can be treated with the combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) (**B1**).
- Treatment-naïve patients with or without cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin (**B2**).
- Based on data with other combinations, treatment-experienced patients with or without compensated cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (**B2**).
- In treatment-experienced patients with or without compensated cirrhosis with contraindications to the use of ribavirin, extending duration of treatment to 24 weeks must be considered (**B2**).

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

Treatment of patients with severe liver disease with or without an indication for liver transplantation and patients in the post-liver transplant setting

Patients with decompensated liver disease had an absolute contraindication to the use of IFN-based regimens. In the post-liver transplant setting, IFN-based therapies could be used, but they induced numerous, often severe side effects, and their results were disappointing. IFN-free, DAA-based regimens now appear as the most suitable options for these patients who need urgent treatment.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

JOURNAL OF HEPATOLOGY

Recommendations

- IFN-free regimens are the only options in HCV-monoinfected and in HIV-coinfected patients with decompensated (Child-Pugh B or C) cirrhosis, with or without an indication for liver transplantation, and in patients after liver transplantation because of their virological efficacy, ease of use and tolerability (**A1**).
- The same IFN-free treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection. Treatment alterations or dose adjustments may be needed in case of interactions with antiretroviral drugs (**B1**).

Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation

Liver transplantation is the treatment of choice for patients with end-stage liver disease. Hepatitis C recurrence due to graft infection is universal after transplantation in the absence of prevention [78], and the life of the graft is reduced in patients with recurrent hepatitis C.

There is an on-going debate as to whether patients with decompensated cirrhosis on the transplant list should be treated for their HCV infection prior to liver transplantation or, conversely, transplanted first and treated promptly after transplantation. Thus far, no consensus has been reached because these two approaches have not been prospectively compared in appropriately powered randomized trials using clinical endpoints. It is unlikely that such trials will be performed. In their absence, the recommendations are guided by the results of clinical trials assessing each approach separately, data from the real-world and the panel members' experience.

Treatment of HCV infection in patients awaiting a liver transplantation has two complementary goals: preventing liver graft infection after transplantation if viral clearance is achieved, and improving liver function before transplantation. Prevention of liver graft infection substantially facilitates post-transplant management. In addition, improvement of liver function implies delisting of some patients [79], an appropriate strategy in the current context of organ shortage [80]. However, the duration of antiviral therapy cannot be predicted in a patient on the waiting list, so the patient may be transplanted before the virus has been cleared. In addition, if delisted, the patient will keep a diseased liver with the risk of subsequent decompensations, HCC occurrence and death and could lose an opportunity to cure both the liver disease and the infection, because HCV infection cure can be achieved by therapy in the vast majority of patients after transplantation.

A proof-of-concept study in patients infected with HCV genotypes 1 and 4 demonstrated that sofosbuvir and ribavirin administered for a few weeks before transplantation prevented HCV graft infection in a majority of treated patients [81]. However, this combination is suboptimal and thus not recommended in patients infected with these genotypes. The use of protease inhibitors is not recommended in patients with Child-Pugh B and contraindicated in patients with Child-Pugh C decompensated cirrhosis, due to substantially higher drug concentrations associated with toxicities in these patients. Protease inhibitors should also not be used in patients with compensated cirrhosis with a history of prior decompensation, as cases of decompensation have been reported on treatment [82,83]. Thus, treatment of patients with decompensated cirrhosis on the transplant list should be based on the combination of sofosbuvir and an NS5A inhibitor, namely ledipasvir, velpatasvir or daclatasvir.

In the SOLAR-1 trial, patients infected with genotype 1 or 4 with decompensated cirrhosis were treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 or 24 weeks with ribavirin. The SVR12 rates were 87% (26/30) and 89% (24/27) after 12 and 24 weeks of therapy, respectively, in Child-Pugh B patients; they were 86% (19/22) and 87% (20/23) after 12 and 24 weeks of therapy, respectively, in Child-Pugh C patients. The MELD and Child-Pugh scores improved in approximately half of treated patients [84]. The design of the SOLAR-2 trial was identical in patients infected with genotype 1 or 4 with decompensated cirrhosis who received the same treatment regimens. The SVR12 rates were 87% (20/23) and 96% (22/23) after 12 and 24 weeks of therapy, respectively, in Child-Pugh B patients; they were 85% (17/20) and 78% (18/23) after 12 and 24 weeks of therapy, respectively, in Child-Pugh C patients. The MELD and Child-Pugh scores improved in approximately half of treated patients [85].

In the ASTRAL-4 study, patients with Child-Pugh B decompensated cirrhosis infected with genotypes 1 to 4 were randomized to receive the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks without ribavirin, for 12 weeks with weight-based dosed ribavirin, or for 24 weeks without ribavirin. The SVR12 rates with these three treatment regimens, respectively, were: 88% (44/50), 94% (51/54) and 93% (51/55) in patients with genotype 1a infection; 89% (16/18), 100% (14/14) and 88% (14/16) in patients with genotype 1b infection; 100% (4/4), 100% (4/4) and 75% (3/4) in patients with genotype 2 infection; 50% (7/14), 85% (11/13) and 50% (6/12) in patients with genotype 3 infection; 100% (4/4), 100% (2/2) and 100% (2/2) in patients with genotype 4 infection. No arm with sofosbuvir, velpatasvir and ribavirin for 24 weeks was included in the study [86]. Of the patients with a baseline MELD score <15, 51% (114/223) had an improved MELD score at week 12 post-treatment, 22% (49/223) had no change in their MELD score, and 27% (60/223) worsened MELD score. Of the patients who had a baseline MELD score $\geqslant$15, 81% (22/27) had an improved MELD score, 11% (3/27) had no change in their MELD score, and 7% (2/27) worsened MELD score [86]).

In a real-world study based on the United Kingdom early access program, patients with decompensated cirrhosis infected with HCV genotype 1 were treated with sofosbuvir and ledipasvir, or with sofosbuvir and daclatasvir, for 12 weeks with or without ribavirin. The SVR12 rates were: 85% (11/13) after 12 weeks of sofosbuvir and ledipasvir without ribavirin; 91% (136/149) after 12 weeks of sofosbuvir and ledipasvir with ribavirin; 50% (2/4) after 12 weeks of sofosbuvir and daclatasvir without ribavirin; and 88% (30/34) after 12 weeks of sofosbuvir and daclatasvir with ribavirin. In patients with decompensated cirrhosis infected with genotype 3, the SVR12 rates were 60% (3/5) after 12 weeks of sofosbuvir and daclatasvir without ribavirin; 71% (75/105) after 12 weeks of sofosbuvir and daclatasvir with ribavirin [87]. Approximately one third of patients improved their MELD scores, one third had no change, and one third suffered deteriorating liver function 12 weeks after treatment. Improvement in MELD score was more frequent in treated than in untreated patients. The proportion of patients with at least one decompensating event during the study period (baseline to week 12 post-treatment) was reduced in the treated compared to untreated group, apart from the subgroup with a baseline

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

MELD score ⩾15. Rates of new decompensation in patients with recompensated disease at baseline were significantly lower in the treated cohort (4% *vs.* 10%) [87]. Longer-term follow-up of the same group of patients confirmed that treatment was clinically beneficial in patients with advanced liver disease [88].

In a multicentre European real-world study, interferon-free, DAA-based therapy reversed liver dysfunction of approximately one patient out of three who were put on hold and the delisting of approximately one patient out of 5 in 60 weeks. Patients with lower MELD scores had higher chances to be delisted. However, the long-term clinical benefit of therapy was not assessed in this study [89]. The short-term benefits observed must be balanced with the respective risks of the liver transplantation and of not being transplanted.

Recommendations

- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18-20 can be treated prior to liver transplantation. 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**).
- Protease inhibitors should not be used in patients with Child-Pugh B or C decompensated cirrhosis (**A1**).
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score <18-20 can be treated with one of the following combinations: sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**A1**).
- Patients with decompensated cirrhosis, no HCC and a MELD score <18-20 infected with HCV genotype 1, 4, 5 or 6 should be treated with sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis, no HCC and a MELD score <18-20 infected with HCV genotype 2 should be treated with sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 12 weeks with ribavirin (**B1**).
- Patients with decompensated cirrhosis, no HCC and a MELD score <18-20 infected with HCV genotype 3 should be treated with sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, for 24 weeks with ribavirin (**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), the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B1**).
- 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**).
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 should be transplanted first, without antiviral treatment. HCV infection should be treated after liver transplantation (**B1**).
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 can be treated before transplantation if the waiting time on the transplant list exceeds 6 months, depending on the local situation (**B1**).

Patients with HCC, without cirrhosis or with compensated cirrhosis, with an indication for liver transplantation

Patients with HCC without cirrhosis or with compensated cirrhosis who have an indication for liver transplantation can be treated for their hepatitis C prior to liver transplantation. Indeed, treatment will not delay transplantation, while preventing recurrence of infection and improving the post-transplant prognosis. In these patients, treatment is similar to that in patients without cirrhosis or with compensated cirrhosis who do not have HCC, and depends on the HCV genotype, prior therapy and severity of liver disease (see general recommendations).

Recommendations

- In patients with HCC awaiting liver transplantation with an indication for antiviral treatment, treatment can be initiated as soon as possible in order to complete a full treatment course before transplantation (**B1**).
- Patients with HCC who have no or compensated (Child-Pugh A) cirrhosis awaiting liver transplantation should be treated prior to liver transplantation, according to the general recommendations in patients with no or compensated cirrhosis and no HCC (**B1**).

Post-liver transplantation recurrence

HCV infection recurrence is universal in patients with detectable HCV RNA at the time of liver transplantation [78]. 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 [90,91]. 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 [92,93].

Early results in HCV infected liver transplant recipients using a combination of sofosbuvir and ribavirin for 24 to 48 weeks showed a beneficial impact of HCV clearance on liver function and patient survival post-liver transplantation. Calcineurin inhibitor dose adjustments were not required due to the lack of significant interactions of sofosbuvir with tacrolimus or cyclosporine [94,95].

In the SOLAR-1 trial, transplant recipients with HCV genotype 1 or 4 recurrence were treated with the fixed-dose combination of sofosbuvir and ledipasvir for 12 or 24 weeks with ribavirin. In patients treated for 12 weeks with ribavirin, the SVR12 rates were 96% (53/55) in those without cirrhosis, 96% (25/26) in those with compensated (Child-Pugh A) cirrhosis, 85% (22/26) in those with Child-Pugh B decompensated cirrhosis, and 60% (3/5) in those with Child-Pugh C decompensated cirrhosis. The SVR12 rates were not higher in patients treated for 24 weeks with ribavirin: 98% (55/56), 96% (24/25), 88% (23/26), and 75% (3/4), respectively [84]). Similar results were reported in the SOLAR-2 study in patients with genotype 1 receiving the same treatment regimens. In patients treated for 12 weeks with ribavirin, the

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

SVR12 rates were 93% (42/45) in patients without cirrhosis, 100% (30/30) in those with compensated (Child-Pugh A) cirrhosis, 95% (19/20) in those with Child-Pugh B decompensated cirrhosis, and 50% (1/2) in those with Child-Pugh C decompensated cirrhosis. In patients treated 24 weeks, the SVR12 rates were: 100% (44/44), 96% (27/28), 100% (20/20), and 80% (4/5), respectively. Twenty-five of the 27 patients infected with genotype 4 achieved SVR12 [85].

In the ALLY-1 trial in liver transplant recipients treated with the combination of sofosbuvir, daclatasvir and ribavirin for 12 weeks, SVR was achieved in 95% (39/41) of genotype 1 and 91% (10/11) of genotype 3 patients [66].

A trial with the fixed-dose combination of sofosbuvir and velpatasvir is on-going in liver transplant recipients with HCV recurrence.

A number of real-world studies reported high SVR rates after treating liver transplant recipients with HCV recurrence with the combination of sofosbuvir and ledipasvir or daclatasvir. For instance, in the TRIO real-world cohort study, SVR12 was achieved in 97% (34/35) of genotype 1 liver recipients treated for 12 weeks without ribavirin and in 100% (19/19) of those treated for 12 weeks with ribavirin [96]. In another study, SVR12 was achieved in 97% (29/30) of patients treated with sofosbuvir and ledipasvir with or without ribavirin for 12 or 24 weeks. In 15 of the 25 patients who received ribavirin, its administration had to be discontinued because of severe anaemia [97]. In the CUPILT cohort study, SVR12 was achieved in 100% (21/21) of patients receiving sofosbuvir and daclatasvir for 12 weeks without ribavirin, 75% (3/4) of those receiving sofosbuvir and daclatasvir for 12 weeks with ribavirin, 97% (67/68) of those receiving sofosbuvir and daclatasvir for 24 weeks without ribavirin, and 95% (42/44) of those receiving sofosbuvir and daclatasvir for 24 weeks with ribavirin. The most common adverse event was anaemia, which increased significantly with the use of ribavirin (18% *vs.* 56%) [98].

Whether ribavirin is needed in all patients after liver transplantation with the fixed-dose combination of sofosbuvir and ledipasvir, the fixed-dose combination of sofosbuvir and velpatasvir, or the combination of sofosbuvir and daclatasvir remains to be determined.

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 [99]. 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 one 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. This combination should not be administered with everolimus. No data with the fixed-dose combination of grazoprevir and elbasvir have been reported in liver transplant recipients. Interactions have been reported with several immunosuppressants that require dose adjustments. In addition, this combination is contraindicated in patients receiving cyclosporine. Similar interactions have been reported with simeprevir. Thus, treatment regimens including a protease inhibitor are not optimal for HCV treatment post-liver transplantation.

Recommendations

- All patients with post-transplant recurrence of HCV infection should be considered for therapy (**A1**).
- Treatment should be initiated early after liver transplantation, ideally as early as possible when the patient is stabilized (generally after the first 3 months post-transplant), because the SVR12 rates diminish in patients with advanced post-transplant liver disease (**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 urgent antiviral treatment (**A1**).
- Patients with post-transplant recurrence of HCV genotype 1, 4, 5 or 6 infection without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis should be treated with the fixed-dose combination of sofosbuvir and ledipasvir, or the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**A1**).
- Patients with post-transplant recurrence of HCV genotype 2 without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis should be treated with the combination of sofosbuvir and daclatasvir for 12 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients with post-transplant recurrence of HCV genotype 3 should be treated with the combination of sofosbuvir and daclatasvir for 24 weeks regardless of the stage of liver disease, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients with post-transplant recurrence of all HCV genotypes without cirrhosis (F0-F3), with compensated (Child-Pugh A) cirrhosis or with decompensated (Child-Pugh B or C) cirrhosis could be treated with the fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks (24 weeks in patients with genotype 3 and decompensated (Child-Pugh B or C) cirrhosis) with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), as soon as the results of on-going studies, particularly drug-drug interactions with immunosuppressant drugs, have been presented (**C2**).
- In patients with decompensated cirrhosis, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**B1**).
- Patients 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), the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B1**).
- The need for ribavirin in post-liver transplant patients without cirrhosis or with compensated (Child-Pugh A cirrhosis) has not been demonstrated and needs further exploration (**C2**).

Patients with decompensated cirrhosis without an indication for liver transplantation

The main goal of anti-HCV therapy in patients with decompensated cirrhosis (Child-Pugh B or C) not on a transplant waiting list is to achieve improvement in liver function and survival. Several studies demonstrated high SVR rates, equivalent in Child-Pugh B and C patients, in individuals with decompensated cirrhosis, together with a clear effect of therapeutic viral clearance on liver function, with significant improvements in bilirubin, albumin and

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

INR values and, as a result, in MELD and Child-Pugh scores in one third to half of patients [66,80,85,86,94]. Similar results were reported in real-world studies [87,89,100,101]. Patients with Child-Pugh B cirrhosis benefited more from viral clearance in terms of adverse event-free survival at 15 months than those with Child-Pugh C cirrhosis [87]. The results of these studies have been summarized above. Long-term clinical follow-up data are lacking.

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 should be treated urgently (**A1**).
- Protease inhibitors should not be used in patients with Child-Pugh B and are contraindicated in patients with Child-Pugh C decompensated cirrhosis (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation should be treated with one of the following combinations: sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation infected with HCV genotype 1, 4, 5 or 6 should be treated with sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation infected with HCV genotype 2 should be treated with sofosbuvir and velpatasvir or sofosbuvir and daclatasvir for 12 weeks with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation infected with HCV genotype 3 should be treated with sofosbuvir and velpatasvir or sofosbuvir and daclatasvir for 24 weeks, with ribavirin (**A1**).
- Patients with decompensated cirrhosis not on the waiting list for liver transplantation 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), the fixed-dose combination of sofosbuvir and velpatasvir (all genotypes), or the combination of sofosbuvir and daclatasvir (all genotypes) for 24 weeks without ribavirin (**B2**).
- Due to the limited amount of safety data reported in patients with decompensated cirrhosis, frequent clinical and laboratory assessment is necessary (**B2**).

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 meta-analyses have examined the relationship between SVR and reduction in the risk of HCC, which suggest that SVR is associated with a reduction in the incidence of HCC in the mid- to long-term [102,103]. However, most of these studies are observational and retrospective and were based on SVR achieved with IFN-based treatments.

IFN has been shown to improve outcomes following ablation or resection of HCV. Whether the high rates of SVR achieved with new IFN-free regimens reduce the risk of recurrence following resection or ablation of HCC is currently debated. Indeed, unexpected early HCC recurrence was reported in two retrospective studies in patients with HCV-related HCC who underwent curative procedures and were subsequently treated with IFN-free regimens and cured from HCV in most cases [104,105]. Because of the small number of patients, the retrospective character of the studies and the lack of control arms, the authors concluded that their observation should be taken as a note of caution and prime a larger scale assessment. Contradictory results were published by other groups, reporting a lack of evidence of an effect of DAA-based regimens on the recurrence of HCC in patients who underwent curative HCC therapy [106–108]. Thus, further data is required to evaluate the impact of highly effective IFN-free regimens on the short-, mid- and long-term 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 recommendations above, according to the HCV genotype, prior therapy and severity of underlying liver disease (unless antiviral therapy proves to be harmful in future studies) (**B2**).

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, but the risk is unpredictable [109]. Patients commencing DAA-based treatment for hepatitis C should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies. If HBs antigen is present or if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients (“occult” hepatitis B), concurrent HBV nucleoside/nucleotide analogue therapy is indicated. Assiduous monitoring of serum aminotransferase levels is indicated in anti-HBs and anti-HBc antibody-positive patients.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

JOURNAL OF HEPATOLOGY

Recommendations

- Patients with HBV coinfection should be treated with the same regimens, following the same rules as HCV monoinfected patients (**B1**).
- If chronic hepatitis B or "occult" HBV infection is detected, 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. Recent studies suggested that SVR induced by IFN-free regimens was associated with improvement of the clinical manifestations of mixed cryoglobulinemia [110,111]. 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. Cases have been reported showing regression of low-grade lymphomas following SVR with an IFN-free regimen [112,113].

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 membrano-proliferative 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, rituximab, plasma exchange, corticosteroids and cyclophosphamide. It is possible but unproven that the effective and rapid antiviral response observed with IFN-free antiviral regimens will improve outcome. Some evidence for rituximab in the management of HCV-induced renal disease exists. An interdisciplinary approach is recommended.

Recommendations

- Antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection, according to the above recommendations. Careful monitoring for adverse events is mandatory (**B1**).
- The indication of rituximab in HCV-related renal disease must be discussed by a multidisciplinary team (**B1**).
- Treatment of HCV-associated lymphoma should utilise IFN-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known (**B1**).

Patients with comorbidities

Patients with renal impairment, including haemodialysis patients

HCV infection is prevalent in patients with renal impairment, including those with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and those with ESRD who require haemodialysis or peritoneal dialysis. Diverse groups of patients with renal disease require consideration when treatment of hepatitis C is indicated. These include patients with chronic kidney disease (CKD) stage 4 with severely reduced renal function (eGFR = 15–29 ml/min/1.73 m^2) or those with CKD stage 5 (eGFR <15 ml/min/1.73 m^2 or on dialysis); post-renal transplant patients; patients with cirrhosis with renal impairment (chronic renal disease, hepatorenal syndrome, acute kidney injury, acute-on-chronic liver failure); post-liver transplant patients with calcineurin-induced renal impairment; or patients with mixed essential cryoglobulinemia with renal damage. In some of these groups, renal function could be potentially improved or worsened with antiviral treatment. Organ recovery may be delayed after an SVR in patients with cryoglobulinemia [111].

In the haemodialysis population, HCV infection 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.

In patients with mild to moderate renal impairment (eGFR $\geqslant$30 ml/min/1.73 m^2), no dose adjustments are necessary for the combinations of sofosbuvir and ribavirin, sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir, grazoprevir and elbasvir, sofosbuvir and daclatasvir or sofosbuvir and simeprevir. These patients should therefore be treated according to the above general recommendations.

In patients with severe renal dysfunction (eGFR <30 ml/min/1.73 m^2), data on the safety and efficacy of sofosbuvir-based regimens are lacking. Sofosbuvir is eliminated mainly by the renal route and its use in CKD stage 4 or 5 or in haemodialysis patients is out of the licence recommendations. Concerns have been raised because of the substantially higher concentrations of sofosbuvir and, most importantly, of its renally excreted metabolite GS-331007 (+171% and +451% $AUC_{0\text{-inf}}$, respectively, as compared with patients without renal impairment). In the TARGET 2.0 real-world cohort study, progressive deterioration of renal function and renal symptoms were reported in patients with severe renal impairment receiving a sofosbuvir-based regimen, although efficacy was comparable to that observed in patients without renal impairment [114]. In patients with ESRD on haemodialysis, the concentrations of GS-331007 were 10-fold higher one hour before dialysis and 20-fold higher one hour after dialysis than in patients with normal renal function [115]. In another study, sofosbuvir and GS-331007 did not accumulate in patients undergoing haemodialysis [116]. Case reports and case series utilising heterogeneous sofosbuvir regimens in patients with renal impairment with varying comorbidities have been reported [110,111,117–121]. However, the data are limited.

Thus, patients with severe renal impairment, or those with ESRD on haemodialysis, can be treated for their HCV infection,

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

but sofosbuvir-free regimens should be preferred whenever possible. The appropriate therapeutic dose of sofosbuvir in patients with advanced renal disease or ESRD is not established. Until such time as the appropriate dosing of sofosbuvir is established, and if treatment is urgent and no sofosbuvir-free regimen is available (as for genotypes 2 and 3 in particular), the risks *vs.* the benefit of sofosbuvir-based regimens should be carefully weighed. Further deterioration in renal function may occur in patients with stage 4 or 5 CKD not on dialysis. For these patients, there is a need to explain the out-of-licence use of sofosbuvir, and thus for informed consent to be obtained. Close monitoring is required and treatment should be rapidly interrupted if the renal function deteriorates. For patients on dialysis, who already have ESRD, the optimal timing of treatment is an important consideration, i.e. pre- or post-renal transplantation if they are candidates for renal transplantation, or the risks *vs.* the benefit if renal transplantation is not possible.

The use of ribavirin is problematic in patients with severe renal impairment or ESRD. 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. In patients who are not candidates for kidney transplantation, the candidacy of a dialysis patient for antiviral therapy requires special consideration of co-morbid conditions, since the liver disease may have relatively little impact on predicted morbidity and mortality of that patient.

Two clinical trials confirmed the efficacy and safety of sofosbuvir-free regimens in patients with severe renal impairment. In the RUBY-1 study, 20 patients infected with genotype 1 without cirrhosis with stage 4 (eGFR 15–30 ml/min/1.73 m^2) or stage 5 (eGFR <15 ml/min/1.73 m^2 or haemodialysis) CKD were treated for 12 weeks with ritonavir-boosted paritaprevir, ombitasvir and dasabuvir. The seven patients infected with genotype 1b were treated without ribavirin, whereas the 13 patients infected with genotype 1a received ribavirin 200 mg once daily. The SVR12 rate was 90% (18/20), with only one patient relapsing after the end of therapy (the other patient died from a cause unrelated to therapy). Nine of 13 patients with genotype 1a infection interrupted ribavirin due to haemoglobin declines that were managed with administration of erythropoietin; ribavirin was resumed in three of them [122].

In the C-SURFER trial, 122 patients infected with HCV genotype 1 (including 6% with cirrhosis) with stage 4 or 5 CKD, including 75% on haemodialysis, were treated with grazoprevir and elbasvir for 12 weeks without ribavirin. The SVR12 rate was 94% (115/122), with only one virological failure. The most common adverse events were headache, nausea, and fatigue, occurring at similar frequencies in patients receiving grazoprevir and elbasvir and in the deferred treatment group receiving placebo. The frequencies of renal system adverse events were generally comparable between treatment groups [123].

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. Studies showing high efficacy and safety of IFN-free anti-HCV regimens in kidney transplant recipients suggest that these patients can be transplanted and treated for their HCV infection after kidney transplantation with a high probability of cure [124–127].

Recommendations

- Patients with mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2) with HCV infection should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored (**A1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and patients with end-stage renal disease on haemodialysis should be treated in expert centres, with close monitoring by a multidisciplinary team (**B1**).
- Sofosbuvir should be used with caution in patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease because no dose recommendation can currently be given for these patients (**B1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 1a should be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or with the combination of grazoprevir and elbasvir for 12 weeks, with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline (**B1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 1b should be treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks or with the combination of grazoprevir and elbasvir for 12 weeks, without ribavirin (**A1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 4 should be treated with the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or with the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).
- In patients receiving ribavirin, haemoglobin levels should be carefully and frequently monitored and ribavirin administration should be interrupted in case of severe anaemia (haemoglobin <8.5 g/dl). The use of erythropoietin and, eventually, blood transfusion, may be useful in patients with severe ribavirin-induced anaemia (**B1**).
- Patients with cirrhosis, and those with a contraindication or who do not tolerate ribavirin, may benefit from 24 weeks of these therapies without ribavirin (**B2**).
- If treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 2, these patients should receive the fixed-dose combination of sofosbuvir and velpatasvir, or the combination of sofosbuvir and daclatasvir for 12 weeks without ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration (**B1**).
- If treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 3, these patients should receive the fixed-dose combination of sofosbuvir and velpatasvir, or the combination of sofosbuvir and daclatasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or for 24 weeks without ribavirin. Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration (**B1**).
- The risks versus benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation require individual assessment (**B2**).

Non-hepatic solid organ transplant recipients

HCV infection in kidney transplant recipients may be associated with an increased rate of liver fibrosis progression. Most cohorts of kidney transplant patients show that HCV positivity is associated with impaired renal graft and patient survival, particularly in patients with cirrhosis. Impaired graft survival partly reflects

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

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 [128]. 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 transplant candidates [79]. For patients with established cirrhosis and portal hypertension who fail (or are unsuitable for) HCV antiviral treatment, consideration must be given to combined liver and kidney transplantation [129]. In a randomized clinical trial, the fixed-dose combination of sofosbuvir and ledipasvir yielded SVR rates of 100% (57/57) and 100% (57/57) in patients infected with HCV genotype 1 or 4 treated 12 or 24 weeks, respectively, without ribavirin. Treatment was well tolerated and no significant changes in eGFR were observed during and after treatment administration [127]. Other real-world studies reported high SVR rates and good safety in patients treated with various treatment regimens post-kidney transplantation [124–126].

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. There is limited experience with the treatment of lung transplant recipients, but sofosbuvir-based regimens appeared to be safe and efficacious in case reports [130]. No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

Experience accumulated with the treatment of liver transplant recipients suggests that these patients can be treated with the expectation of high SVR rates and acceptable safety. Combinations of sofosbuvir with an NS5A inhibitor, such as ledipasvir, velpatasvir or daclatasvir, should be utilised because they do not require immunosuppressant drug dose adjustments (with the probable exception of everolimus).

Recommendations

- Solid organ transplant recipients, including kidney, heart, lung, pancreas or small bowel recipients should be treated for their HCV infection after transplantation, provided that their life expectancy exceeds one year (**A1**).
- Patients infected with HCV genotype 1, 4, 5 or 6 infection should be treated with the fixed-dose combination of sofosbuvir and ledipasvir, the fixed-dose combination of sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in on-going studies), or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients infected with HCV genotype 2 should be treated with the fixed-dose combination of sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in on-going studies) or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).
- Patients infected with HCV genotype 3 should be treated with the fixed-dose combination of sofosbuvir and velpatasvir (if the drug-drug interaction profile with immunosuppressants is favourable in on-going studies) or the combination of sofosbuvir and daclatasvir according to the general recommendations, without the need for immunosuppressant drug dose adjustments (with the probable exception of everolimus) (**B1**).

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 [131,132]. The prevalence of HCV among PWIDs is approximately 65% [133–135] and >80% among long-term PWIDs [133].

HCV treatment must be considered for PWIDs who are willing to receive treatment, are able and willing to maintain regular appointments and adherence, and accept to undergo integrated management of their substance abuse, including syringe exchange program, substitution therapy and other general harm reduction strategies. Guidelines for pre-therapeutic assessment and care of HCV infected PWIDs are available [38,136]. Modelling studies suggest that implementation of HCV treatment for PWIDs could reduce transmission when combined with preventive measures [137–139]. Composite screening, linkage to care and treatment, together with harm reduction programs, are urgently required for this important reservoir. 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.

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 have not been presented on clinical trial sub-populations of individuals on opioid substitution therapy. In a Phase II study, patients infected with HCV genotype 1 without cirrhosis who were treatment-naïve and on chronic methadone or buprenorphine substitution were treated with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks with ribavirin. The SVR rate was 97% (37/38) [140]. In the C-EDGE CO-STAR trial, treatment-naïve patients on opioid substitution for at least 3 months were treated with grazoprevir and elbasvir for 12 weeks without ribavirin. The SVR12 rates were 93% (144/154) in genotype 1a patients, 93% (28/30) in genotype 1b patients, and 92% (11/12) in genotype 4 patients. Study medication adherence was high and safety was not different from that in the placebo arm [141]. Studies are on-going with other treatment regimens in PWIDs on opioid substitution.

Some drug-drug interaction studies have been undertaken between individual DAAs and either methadone or buprenorphine. The only potentially clinically important interaction observed is between ritonavir-boosted paritaprevir and ombitasvir plus dasabuvir with buprenorphine, with a recommendation to monitor closely. However, given that actual pharmacokinetic interaction data are not available for all the DAA regimens with both methadone and buprenorphine, it is prudent to monitor for signs of opioid toxicity.

In addition to opioid substitution therapy, antidepressants, antipsychotics and sedatives are frequently used by patients with addiction problems. There is a lack of formal pharmacokinetic studies between many of the psychoactive drugs and DAAs. Escitalopram and citalopram have been studied and either of these

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

drugs can be safely combined with HCV treatment [142]. Ritonavir-boosted paritaprevir and ombitasvir with dasabuvir are most likely to cause drug interactions via the inhibition of CYP3A4. Caution is thus warranted when drugs with a narrow therapeutic index, such as midazolam and quetiapine, are co-administered with these DAAs. Pharmacokinetic studies on recreational and illicit drug use have not been performed.

Reinfection rates will require reporting and monitoring, and appropriate interventions to limit retreatment will be necessary.

Recommendations

- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and if negative, annually (**A1**).
- 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 on-going 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**).
- 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 (**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 contraindication 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 or thalassemia, with a more rapid course of liver disease because of the concurrent iron overload [143]. Treatment has often been withheld in these patients because both pegylated IFN-α and ribavirin can cause anaemia. Few trials with antiviral therapy have been published in this population, but there is no reason to consider that HCV DAAs are specifically contraindicated. For instance, in the C-EDGE IBLD study, the fixed-dose combination of grazoprevir and elbasvir was administered for 12 weeks without ribavirin in patients with haemoglobinopathies infected with genotypes 1a, 1b or 4. Approximately one patient out of four had cirrhosis. Patients with a haemoglobin level <7 g/dL were excluded. SVR12 was achieved in 95% (18/19) of patients with sickle cell anaemia and in 98% (40/41) of patients with β-thalassemia [144]. On treatment, haemoglobin levels were maintained. Thus, IFN-free, ideally ribavirin-free drug regimens should be used in these patients because they have the great advantage of not aggravating the anaemia. Sofosbuvir-based studies in this group are in progress.

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 transfusion support 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. 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. The management of chronic hepatitis C in haemophilia is similar to the non-haemophilic population and HCV DAAs are applicable to patients with haemophilia. In a study with the fixed-dose combination of grazoprevir and elbasvir administered for 12 weeks without ribavirin, SVR12 was achieved in 91% (42/46) of patients with von Willebrand disease or haemophilia A or B [144].

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 contraindication to liver transplantation in haemophilia. The indications for liver transplantation in

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

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 coinfected patients receiving antiretroviral agents requires careful selection of agents (**A1**).

Treatment monitoring

Treatment monitoring includes monitoring of treatment efficacy, of safety and side effects and of drug-drug interactions.

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 [145–147]. Measurements of HCV core antigen levels by means of ELISA can be used as an alternative to HCV RNA level measurements in settings where HCV RNA assays are not available or not affordable [11,12,23].

In order to monitor treatment efficacy, HCV RNA (or HCV core antigen) level measurements should be performed at specific time points. Measurements should be made to assess patient adherence to therapy. In all cases, HCV RNA (or HCV core antigen) level monitoring indicates whether treatment has been successful.

Recommendations

- A real-time PCR-(or TMA)-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**).
- Measurement of HCV core antigen levels by EIA can be used as an alternative to HCV RNA level measurement to monitor treatment efficacy during and after therapy when HCV RNA assays are not available or not affordable (**A1**).
- In patients treated with an IFN-free regimen, HCV RNA or HCV core antigen levels should be measured at baseline, between week 2 and 4 for assessment of adherence (optional), at end-of-treatment (week 8, 12, 16 or 24 in patients treated 8, 12, 16 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively) (**A2**).
- Monitoring of treatment efficacy can be simplified in order to improve access to care by measuring HCV RNA or HCV core antigen levels only at baseline and 12 or 24 weeks after the end of therapy (SVR12 or SVR24, respectively) (**A2**).

Monitoring of treatment safety

New DAA regimens are generally well tolerated. Frequencies of high grade or severe 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.

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. A few cases of severe pulmonary arterial hypertension have been reported in patients receiving sofosbuvir-based regimens, but a causal link has not been firmly established [148].

Sofosbuvir and velpatasvir

The proportion of patients who permanently discontinued treatment due to adverse events during treatment was <1% for patients receiving sofosbuvir and velpatasvir for 12 weeks.

In clinical studies, no difference with placebo-containing arms was observed. Fatigue and headache were the most common adverse events in patients treated with sofosbuvir and velpatasvir. When sofosbuvir and velpatasvir 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 with and without ribavirin, related to the inhibition of bilirubin trans-

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

porters 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.

Grazoprevir and elbasvir

Severe adverse events were observed in 2.4% and 2.6% of patients receiving grazoprevir and elbasvir without or with ribavirin, respectively. They led to treatment interruptions in 0.1 and 0.3% of cases, respectively. The overall tolerability profile was more favourable in patients not receiving ribavirin in combination with grazoprevir and elbasvir. The most frequent adverse events were fatigue, headache, and nausea, not more frequent than in placebo-containing arms. During the Phase II and III trials, 0.8% (13/1690) of patients experienced asymptomatic ALT elevations up to >5 times the upper limit of normal, on average 10 weeks after the start of treatment. These events resolved spontaneously with continued therapy or end of treatment. Three patients (0.18%) discontinued due to ALT elevation.

Daclatasvir

The overall safety profile of daclatasvir in combination with sofosbuvir suggests that the most common adverse reactions related to this drug are fatigue, headache and nausea. When sofosbuvir and daclatasvir 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.

Simeprevir

The most common adverse reactions reported during 12 weeks of treatment with simeprevir in combination with sofosbuvir were fatigue, headache, nausea, insomnia and pruritus. 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. The safety and efficacy of simeprevir has not been studied in HCV infected patients with severe renal impairment or ESRD, including patients requiring dialysis.

Ribavirin

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

- The patients receiving an IFN-free regimen should be assessed for clinical side effects at each visit (**A1**).
- Haematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter in patients receiving ribavirin (**A1**).
- ALT levels should be assessed at weeks 4, 8 and 12 of therapy, and at week 24 in patients receiving 24 weeks of treatment, as well as at 12 or 24 weeks post-treatment (**A1**).
- Renal function should be checked regularly in patients receiving sofosbuvir, especially in those with reduced eGFR (**A1**).
- Monitoring for rashes and indirect bilirubin elevations without ALT elevations should be performed in patients receiving simeprevir (**A1**).
- Monitoring for indirect bilirubin increases should be performed in patients receiving the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (**A1**).
- No dose adjustment of sofosbuvir and ledispavir, velpatasvir, daclatasvir or simeprevir is required in patients with mild, moderate or severe renal impairment (**B1**).
- The use of sofosbuvir is not recommended in patients with eGFR <30 ml/min/1.73 m^2. If no other option is available and treatment is urgently needed, the appropriate dose of sofosbuvir is not yet established; thus close monitoring of renal function is required and treatment should be interrupted if the renal function deteriorates (**B1**).
- No dose adjustment of sofosbuvir and ledipasvir, velpatasvir or daclatasvir is required for patients with mild (Child-Pugh A), moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment (**A1**).
- Higher exposures have been observed with the protease inhibitors in patients with severe hepatic impairment and their use is not recommended in patients with Child-Pugh B and contraindicated in patients with Child-Pugh C decompensated cirrhosis (**B1**).
- 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**).
- An increase in ALT levels on treatment should prompt a test for HBs antigen and/or HBV DNA (**B1**).

Monitoring of drug-drug interactions

The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment. 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**).

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Treatment dose reductions

If significant anaemia occurs (haemoglobin <10 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 [149–157].

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 and ledipasvir, velpatasvir, daclatasvir, simeprevir, ritonavir-boosted paritaprevir plus ombitasvir and dasabuvir or grazoprevir and elbasvir. 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.

Recommendations

- The dose of ribavirin should be adjusted downward by 200 mg at decrements if the haemoglobin level drops below 10 g/dl. Ribavirin administration should be stopped if the haemoglobin levels drops below 8.5 g/dl (**A1**).
- Treatment should be promptly stopped in case of ALT flare >10 times the upper limit of normal values (**A1**).
- Treatment should be promptly stopped in case of severe bacterial infection at any site, regardless of the neutrophil count, especially in patients with decompensated cirrhosis (**A1**).
- Treatment should be stopped in case of severe adverse events of unclear origin (**B2**).

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 selection of RASs, 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 rare side effects to be expected during treatment. 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 [158,159]. 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 pre-treatment assessment and preparation, as well as to on-treatment adherence monitoring and support, which has become easier with the new IFN-free regimens. Assessment tools utilised in chronic disease are available [160].

Alcohol consumption has an impact on treatment adherence [161]. 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 [161–164]. 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 and patient activation assessment 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 should be considered 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 (or HCV core antigen if HCV RNA testing is not available or not affordable) at 48 weeks post-treatment. If HCV RNA (or HCV core antigen) is still not detected, the infection can be considered as definitely cured and HCV RNA does not need to be retested. Patients with pre-existing cofactors for liver disease (notably, history of alcohol drinking, obesity 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 (like patients with advanced fibrosis, METAVIR score F3), and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy (though first variceal bleed is seldom observed after

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

SVR). The presence of cofactors for liver disease, such as history of alcohol drinking, obesity and/or type 2 diabetes, may determine that additional assessments are necessary. 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 [3,4]. Thus, the duration of HCC surveillance in patients with advanced fibrosis or cirrhosis who achieve an SVR is indefinite.

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 PWID or men who have sex with men, are in the order of 1–8% per year [165–169]. The ease of IFN-free therapy may increase the likelihood of reinfection, as recently suggested [170]. 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 (or HCV core antigen) at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative (**A1**).
- Patients with advanced fibrosis (F3) and cirrhotic patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (**A1**).
- 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 (**A1**).
- The risk of reinfection should be explained, to positively modify risk behaviour (**A1**).
- 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 (**A1**).

Retreatment of non-sustained virological responders

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

Treatment of patients who failed to achieve SVR after treatment with pegylated IFN-α and ribavirin alone is described in the above general recommendations.

Retreatment of genotype 1 patients who failed after a triple combination of pegylated IFN-α, ribavirin, and telaprevir, boceprevir or simeprevir

Patients exposed to a protease inhibitor in combination with pegylated IFN-α and ribavirin should be retreated with a combination of sofosbuvir and an NS5A inhibitor (i.e. 2 compounds without cross-resistance with the protease inhibitor).

In the ION-2 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 [41]. 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 [41]. 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 [48].

In the ASTRAL-1 study, the SVR12 rate was 100% (48/48) in patients exposed to a protease inhibitor in combination with pegylated IFN-α and ribavirin retreated with sofosbuvir and velpatasvir for 12 weeks, without ribavirin. 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 [64].

Retreatment of patients who failed after an IFN-free regimen (all genotypes)

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 [30,50]. Thus, retreatment strategies should include sofosbuvir. In contrast, patients exposed to a protease inhibitor (paritaprevir, grazoprevir, simeprevir), an NS5A inhibitor (ledipasvir, velpatasvir, ombitasvir, elbasvir, daclatasvir) or a non-nucleoside inhibitor of HCV polymerase (dasabuvir) who fail to achieve SVR select viruses with RASs in the NS3 protease, NS5A and polymerase regions, respectively. Viruses resistant to protease 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 [30,50].

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 to three other drugs, ideally with no cross-resistance with the drugs already administered. Retreatment should be for 12 weeks with ribavirin, or extended to 24 weeks with ribavirin in more difficult-to-cure patients, such as patients with F3 fibrosis or cirrhosis, or 24 weeks without ribavirin for those who have a contraindication or do not tolerate ribavirin.

Currently, only a few studies including a small number of selected patients support these retreatment recommendations, which are mostly based on indirect evidence. In a study, retreatment with 12 weeks of sofosbuvir plus ledipasvir with ribavirin

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

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 pegylated IFN-α and ribavirin [171]. In another study, 15 patients who failed to achieve SVR after treatment containing an NS5A inhibitor were retreated with sofosbuvir and simeprevir for 12 weeks without ribavirin. SVR12 was achieved in 8/10 patients with genotype 1a, 3/3 patients with genotype 1b, and 2/2 patients with genotype 4 [172]. Ten patients with F3 fibrosis or compensated cirrhosis who failed to achieve SVR after an IFN-free regimen were retreated with the triple combination of sofosbuvir, simeprevir and daclatasvir with ribavirin for 24 weeks. Six of them achieved SVR12, two relapsed after retreatment, and two patients experienced severe adverse events leading to treatment discontinuation, including one patient who died from acute-on-chronic liver failure [173].

Patients treated with the fixed-dose combination of sofosbuvir and velpatasvir for 4 to 12 weeks who failed to achieve SVR were retreated with the same combination for 24 weeks with ribavirin. Among them, SVR12 was achieved in 97% (33/34) of patients infected with genotype 1, 91% (13/14) of patients infected with genotype 2 and 76% (13/17) of patients infected with genotype 3 [174].

In the QUARTZ-1 study, 20 patients infected with genotype 1 with a history of previous DAA treatment failure without discontinuation for reasons other than virological failure were treated with a combination of sofosbuvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 or 24 weeks, with or without ribavirin. SVR12 was achieved in 13/14 patients with genotype 1a infection without cirrhosis treated for 12 weeks with ribavirin, in 6/6 patients infected with genotype 1a with cirrhosis treated for 24 weeks with ribavirin, and in 2/2 patients infected with genotype 1b treated for 12 weeks without ribavirin [175]. In C-SWIFT-RETREATMENT, patients infected with genotype 1 exposed to a short treatment (4, 6 or 8 weeks) with the combination of sofosbuvir, grazoprevir and elbasvir without ribavirin were retreated with the same drug combination with ribavirin for 12 weeks. All of them (23/23) achieved SVR.

Whether 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. Table 8 summarizes the RASs that have been shown to confer reduced susceptibility to the corresponding drug class *in vitro* and/or that have been reported to be selected by IFN-free therapies in patients who failed to achieve SVR. These many RASs and a number of alternative substitutions at the same positions can be present at retreatment baseline in patients previously exposed to DAAs. In the current state of knowledge, no specific algorithms can be derived from these observations to guide retreatment decisions. Thus, retreatment must be guided either by the knowledge of which drugs were administered in previous treatment courses if no resistance test is available or, if resistance testing is performed, by probabilities of response according to the resistance profile observed and the treating team's experience. Preliminary data in a small number of patients suggests that retreatment can be optimized based on RAS testing [176].

Table 9 summarizes the available retreatment options according to the HCV genotype and previous treatment.

Recommendations

- Patients who failed after pegylated IFN-α and ribavirin combination treatment must be retreated according to the above recommendations by HCV genotype (**A1**).
- Patients infected with HCV genotype 1 who failed after a triple combination regimen of pegylated IFN-α, ribavirin and telaprevir, boceprevir or simeprevir should be retreated with the IFN-free combination of sofosbuvir and ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir, with ribavirin for 12 weeks (**A1**).
- Patients who failed on a DAA-containing regimen should be retreated with an IFN-free regimen for 12 weeks with weight-based ribavirin if they have no, mild or moderate fibrosis (METAVIR score F0 to F2), for 24 weeks with ribavirin if they have extensive fibrosis (F3) or cirrhosis, unless otherwise specified below (**B1**).
- Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus pegylated IFN-α and ribavirin can be retreated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 or 6), sofosbuvir and velpatasvir (all genotypes), ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), ritonavir-boosted paritaprevir and ombitasvir (genotype 4), grazoprevir and elbasvir (genotypes 1 or 4; 24 weeks in F0-F2 patients with HCV RNA >800,000 IU/ml), sofosbuvir plus daclatasvir (all genotypes), or sofosbuvir plus simeprevir (genotype 4) (**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 ledipasvir, sofosbuvir and velpatasvir, or sofosbuvir and daclatasvir (**B1**).
- Patients infected with HCV genotype 1 or 4 who failed on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir, ombitasvir, elbasvir or daclatasvir, should be retreated with a combination of sofosbuvir, ritonavir-boosted paritaprevir, ombitasvir and dasabuvir (genotype 1), with a combination of sofosbuvir, ritonavir-boosted paritaprevir and ombitasvir (genotype 4), with a combination of sofosbuvir, grazoprevir and elbasvir (genotypes 1 and 4) or with a combination of sofosbuvir, simeprevir and daclatasvir (genotypes 1 or 4), for 12 weeks (genotype 1b or 4 patients with METAVIR score F0 to F2) or 24 weeks (all patients with genotype 1a; genotype 1b and 4 patients with METAVIR score F3 or with compensated cirrhosis) with ribavirin. Treatment should be administered with caution in patients with extensive fibrosis (METAVIR score F3) or compensated cirrhosis due to a possible risk of severe adverse events of some of these combinations (**B1**).
- Patients infected with HCV genotype 2, 3, 5 or 6 who failed on a regimen containing an NS5A inhibitor, such as ledipasvir, velpatasvir or daclatasvir, should be retreated with a combination of sofosbuvir and velpatasvir for 24 weeks with ribavirin (**B1**).
- Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available (**A1**).
- The utility of HCV resistance testing prior to retreatment in patients who failed on any of the DAA-containing treatment regimens is unknown. If reliable resistance testing is performed, retreatment can be guided by probabilities of response according to the resistance profile observed in the context of an experienced multidisciplinary team (**B2**).

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 [25]. Patients with advanced fibrosis (METAVIR score F3) and cirrhosis should undergo specific ultrasound surveillance for every 6 months.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

Table 8. RASs shown to confer reduced susceptibility to the corresponding drug classes in *in vitro* assays and/or selected in patients who failed to achieve SVR on IFN-free regimens. These RASs and a number of other substitutions at the same positions may be present at retreatment baseline in patients who failed to achieve SVR, suggesting reduced susceptibility to drug(s) from the corresponding class(es) that may help guide retreatment decisions. Adapted from [30].

Drug class	Amino acid position	Genotype/subtype						
		1a	1b	2	3	4	5	6
Nucleotide analogue (sofosbuvir)	159	L159F	L159F	L159F	L159F			
	282	S282T/R	S282T	S282T	S282T	S282T	S282T	
	320	L320I/F/V						
	321	V321A			V321A			
NS5A inhibitors	24	K24G/N/R		T24A				Q24H
	26	K26E						
	28	M28A/G/T/S/V	L28M/T	L/F28M/V/S	M28T	L28S/V	L28I	F28L
	29		P29S					
	30	Q30C/D/E/G/H/I/K/L/Q/R/S/T/Y	R30G/H/P/Q/R	L30H/S	A30K/S	L30H		
	31	L31I/F/M/P/V	L31F/I/M/V	L31M/V	L31I/M/V	L31I/M	L31V	L31M/V
	32	P32L/S	P32F/L/S					P32L/S
	38	S38F						
	58	H58D/L/R	P58D/S			T58P/S		T58A/N/S
	62		Q/E62D					
	92	A92K/T	A92K					
	93	Y93C/F/H/L/N/R/S/T/W	Y93C/H/N/S	Y93H	Y93H	Y93H/R		V36I
Protease inhibitors	36	V36A/C/G/L/M	V36A/C/G/L/M					
	41	Q41R	Q41R					
	43	F43L	F43I/S/V					
	54	T54A/S	T54A/C/G/S					
	55	V55A/I	V55A					
	56	Y56H	Y56H/L	Y56H		Y56H		Y56H
	80	Q80H/K/L/R	Q80H/K/L/R					L80K/Q
	122	S122G/R	S122D/G/I/N/R/T					S122T
	155	R155G/I/K/M/S/T/W	R155C/G/I/K/Q/M/S/T/W					
	156	A156S/T/V	A156G/F/S/T/V					
	158	V158I	V158I					
	168	D168A/C/E/F/G/H/I/K/L/N/T/V/Y	D168A/C/E/F/G/H/I/K/L/N/T/V/Y		Q168R	D168V		D168E/Y
	170	I/V170F/T/V	I/V170A/L/T					I170V
	175		M175L					
Non-nucleoside palm-1 inhibitor (dasabuvir)	314	L314H						
	316	C316Y	C316H/N/Y/W					
	368		S368T					
	411		N411S					
	414	M414I/T/V	M414I/T/V					
	445		C445F/Y					
	446	E446K/Q						
	448	Y448C/H	Y448C/H					
	451	C451R						
	553	A553T	A553V					
	554	G554S	G554S					
	555	Y555H						
	556	S556G/R	S556G/R					
	557	G557R						
	558	G558R	G558R					
	559	D559G/N	D559G/N					
	561	Y561H/N						

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Table 9. Treatment recommendations for retreatment of HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C who failed to achieve an SVR on prior antiviral therapy containing one or several DAA(s). 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.

Failed treatment	Geno-type	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ Elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir	Sofosbuvir plus grazoprevir/ elbasvir	Sofosbuvir plus daclatasvir plus simeprevir
PegIFN-α with ribavirin and telaprevir, or boceprevir, or simeprevir	1	12 wk with ribavirin	12 wk with ribavirin	No	No	No	12 wk with ribavirin	No	No	No	No	No
Sofosbuvir alone, or sofosbuvir plus ribavirin, or sofosbuvir plus PegIFN-α and ribavirin	1	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2 with HCV RNA ≤800,000 (5.9 log) IU/ml) or 24 wk with ribavirin (F0-F2 with HCV RNA >800,000 (5.9 log) IU/ml and F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No
	2	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	3	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	4	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2 with HCV RNA ≤800,000 (5.9 log) IU/ml) or 24 wk with ribavirin (F0-F2 with HCV RNA >800,000 (5.9 log) IU/ml and F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Table 9 (*continued*)

Failed treatment	Genotype	Sofosbuvir/ledipasvir	Sofosbuvir/velpatasvir	Ombitasvir/paritaprevir/ritonavir and dasabuvir	Ombitasvir/paritaprevir/ritonavir	Grazoprevir/Elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir	Sofosbuvir plus ombitasvir/paritaprevir/ritonavir and dasabuvir	Sofosbuvir plus ombitasvir/paritaprevir/ritonavir	Sofosbuvir plus grazoprevir/elbasvir	Sofosbuvir plus daclatasvir plus simeprevir
Sofosbuvir alone, or sofosbuvir plus ribavirin, or sofosbuvir plus PegIFN-α and ribavirin	5 or 6	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
Sofosbuvir and simeprevir	1	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	4	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
NS5A inhibitor-containing regimen (ledipasvir, velpatasvir, ombitasvir, elbasvir, daclatasvir)	1a	No	No	No	No	No	No	No	24 wk with ribavirin	No	24 wk with ribavirin	24 wk with ribavirin
	1b	No	No	No	No	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)
	2	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No
	3	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No
	4	No	No	No	No	No	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)
	5 or 6	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

JOURNAL OF HEPATOLOGY

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 of 1 to 2 years (**A1**).
- HCC surveillance every 6 months must be continued indefinitely in patients with advanced fibrosis (F3) and cirrhosis (**A1**).

Treatment of acute hepatitis C

Most patients with acute hepatitis C are asymptomatic, but a high rate of chronicity is expected (50–90%). Symptomatic disease with jaundice, female gender, a young age, and genetic polymorphisms in the region upstream of the *IL28B* (recently renamed IFN lambda-3, *IFNL3*) 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. 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 [177–180].

High SVR rates (>90%) have been reported in a small number of patients with sofosbuvir-based IFN-free regimens. The ideal duration of treatment of acute hepatitis C with IFN-free regimens remains unknown. Three trials were performed with the fixed-dose combination of sofosbuvir and ledipasvir in patients infected with genotype 1. The SVR rates were: 93% (13/14) after 4 weeks of treatment in injection drug users [181], 77% (20/26) after 6 weeks of treatment in HIV-positive individuals [182], and 100% (20%) after 6 weeks of treatment in HIV-negative, non-injection drug users [183]. Because of the small number of patients included in these trials, of the differences in their results, and by analogy with chronic hepatitis C for which at least 8 weeks of therapy are required to maximize SVR rates, patients with acute hepatitis C should be treated with the combination of sofosbuvir and an NS5A inhibitor for 8 weeks, pending additional data establishing the ideal treatment regimen and duration.

There is currently no indication for antiviral therapy as post-exposure prophylaxis in the absence of documented HCV transmission.

Recommendations

- Patients with acute hepatitis C should be treated with a combination of sofosbuvir and ledipasvir (genotypes 1, 4, 5 and 6), a combination of sofosbuvir and velpatasvir (all genotypes), or a combination of sofosbuvir and daclatasvir (all genotypes) for 8 weeks without ribavirin (**B1**).
- Patients with acute hepatitis C and HIV coinfection and/or a baseline HCV RNA level >1 million IU/ml (6.0 log IU/ml) may need to be treated for 12 weeks with the same combination regimens (**B2**).
- SVR should be assessed at 12 and 24 weeks post-treatment, because late relapses have been reported (**B2**).
- 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 will reach the market within the next two years. 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: Abbvie, and Gilead.
- Advisory Boards: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.
- Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

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

David Back:
- Grant and research support: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Viiv.
- Advisory Boards: Abbvie, Gilead, Janssen, and Merck.
- Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

Geoffrey Dusheiko:
- Grant and research support: Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, and Merck.
- Advisory Boards: Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, and Merck.
- Speaking and teaching: Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, and Merck.

Xavier Forns:
- Grant and research support: Abbvie, and Janssen.
- Advisory Boards: Abbvie, Gilead, and Janssen.

Francesco Negro
- Grant and research support: AbbVie, and Gilead.
- Advisory Boards: AbbVie, Bristol-Myers Squibb, Gilead, and Merck.
- Speaking and teaching: Bristol-Myers Squibb, and Merck.

Massimo Puoti:
- Grant and research support: Gilead.
- Advisory Boards: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.
- Speaking and teaching: Bristol-Myers Squibb, Gilead, Janssen, and Merck.

Christoph Sarrazin:
- Grant and research support: Abbott Molecular, Abbvie, Gilead, Janssen, Qiagen, Roche, and Siemens.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

- Advisory Boards: Abbott Molecular, Abbvie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.
- Speaking and teaching: Abbott Molecular, Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck, Qiagen, and Siemens.

References

[1] Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011;17:107–115.
[2] Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77–87.
[3] Arase Y, Kobayashi M, Suzuki F, Suzuki Y, Kawamura Y, Akuta N, et al. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. Hepatology 2013;57:964–973.
[4] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584–2593.
[5] Bruno S, Di Marco V, Iavarone M, Roffi L, Crosignani A, Calvaruso V, et al. Survival of patients with HCV cirrhosis and sustained virologic response is similar to the general population. J Hepatol 2016;64:1217–1223.
[6] Negro F, Forton D, Craxi A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345–1360.
[7] Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719–725.
[8] Chevaliez S, Pawlotsky JM. Diagnosis and management of chronic viral hepatitis: antigens, antibodies and viral genomes. Best Pract Res Clin Gastroenterol 2008;22:1031–1048.
[9] Kamili S, Drobeniuc J, Araujo AC, Hayden TM. Laboratory diagnostics for hepatitis C virus infection. Clin Infect Dis 2012;55:S43–S48.
[10] Bulteel N, Partha Sarathy P, Forrest E, Stanley AJ, Innes H, Mills PR, et al. Factors associated with spontaneous clearance of chronic hepatitis C virus infection. J Hepatol 2016;65:266–272.
[11] Chevaliez S, Feld J, Cheng K, Wedemeyer H, Sarrazin C, Maasoumy B, et al. Clinical utility of HCV core antigen detection and quantification in the diagnosis and management of patients with chronic hepatitis C receiving an all-oral, interferon-free regimen. Antivir Ther 2016, [Epub ahead of print].
[12] Chevaliez S, Soulier A, Poiteau L, Bouvier-Alias M, Pawlotsky JM. Clinical utility of hepatitis C virus core antigen quantification in patients with chronic hepatitis C. J Clin Virol 2014;61:145–148.
[13] Chhatwal J, Wang X, Ayer T, Kabiri M, Chung RT, Hur C, et al. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. Hepatology 2016, [Epub ahead of print].
[14] Pawlotsky JM. The end of the hepatitis C burden: really? Hepatology 2016, [Epub ahead of print].
[15] Chevaliez S, Poiteau L, Rosa I, Soulier A, Roudot-Thoraval F, Laperche S, et al. Prospective assessment of rapid diagnostic tests for the detection of antibodies to hepatitis C virus, a tool for improving access to care. Clin Microbiol Infect 2016;22:459 e451–e456.
[16] Khuroo MS, Khuroo NS, Khuroo MS. Diagnostic accuracy of point-of-care tests for hepatitis C virus infection: a systematic review and meta-analysis. PLoS One 2015;10 e0121450.
[17] Shivkumar S, Peeling R, Jafari Y, Joseph L, Pant Pai N. Accuracy of rapid and point-of-care screening tests for hepatitis C: a systematic review and meta-analysis. Ann Intern Med 2012;157:558–566.
[18] Poiteau L, Soulier A, Rosa I, Roudot-Thoraval F, Hezode C, Pawlotsky JM, et al. Performance of rapid diagnostic tests for the detection of antibodies to hepatitis C virus in whole blood collected on dried blood spots. J Viral Hepat 2016;23:399–401.
[19] Soulier A, Poiteau L, Rosa I, Hezode C, Roudot-Thoraval F, Pawlotsky JM, et al. Dried blood spots: a tool to ensure broad access to hepatitis C screening, diagnosis, and treatment monitoring. J Infect Dis 2016;213:1087–1095.
[20] Tuaillon E, Mondain AM, Meroueh F, Ottomani L, Picot MC, Nagot N, et al. Dried blood spot for hepatitis C virus serology and molecular testing. Hepatology 2010;51:752–758.
[21] Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, Leclere L, et al. Twelve weeks post-treatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology 2010;51:1122–1126.
[22] Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010;139:1593–1601.
[23] Freiman JM, Tran TM, Schumacher SG, White LF, Ongarello S, Cohn J, et al. Hepatitis C core antigen testing for diagnosis of hepatitis C virus infection: a systematic review and meta-analysis. Ann Intern Med 2016, [Epub ahead of print].
[24] Aghemo A, Degasperi E, De Nicola S, Bono P, Orlandi A, D'Ambrosio R, et al. Quantification of core antigen monitors efficacy of direct-acting antiviral agents in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol 2016;14:1331–1336.
[25] European Association for Study of the LiverAsociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–264.
[26] Castera L, Sebastiani G, Le Bail B, de Ledinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J Hepatol 2010;52:191–198.
[27] Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343–350.
[28] Chevaliez S, Bouvier-Alias M, Brillet R, Pawlotsky JM. Hepatitis C virus (HCV) genotype 1 subtype identification in new HCV drug development and future clinical practice. PLoS One 2009;4 e8209.
[29] Fourati S, Pawlotsky JM. Virologic tools for HCV drug resistance testing. Viruses 2015;7:6346–6359.
[30] Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. Gastroenterology 2016;151:70–86.
[31] Terrault NA, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated of sustained virologic response. Gastroenterology 2016, [Epub ahead of print].
[32] Huisman MT, Snoeys J, Monbaliu J, Martens MA, Sekar VJ, Raoof A. In vitro studies investigating the mechanism of interaction between TMC435 and hepatic transporters. Hepatology 2010;52:461A–462A.
[33] Mauss S, Buggish P, Boker KHW, Schott E, Klinker H, Gunther R, et al. Treatment outcomes for hepatitis C genotype 1 infection with direct acting antivirals: data from the German Hepatitis C Registry. J Hepatol 2016;64: S820.
[34] Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, et al. Effectiveness of simeprevir plus sofosbuvir, with or without ribavirin, in real-world patients with HCV genotype 1 infection. Gastroenterology 2016;150:419–429.
[35] Jensen DM, O'Leary JG, Pockros PJ, Sherman KE, Kwo PY, Mailliard ME, et al. Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. Hepatology 2014;60:219A.
[36] Dieterich D, Bacon BR, Flamm SL, Kowdley KV, Milligan S, Tsai N, et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network: academic and community treatment of a real-world, heterogeneous population. Hepatology 2014;60:220A.
[37] European Association for Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015;63:199–236.
[38] EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. J Hepatol 2011;55:245–264.
[39] EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. J Hepatol 2014;60:392–420.
[40] Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–1898.
[41] Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014;370:1483–1493.
[42] Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014;370:1879–1888.
[43] Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015;373:705–713.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

[44] Curry M, Modi AA, Pungpapong S, Leise M, Aqel B, LLewellyn J, et al. Real-world effectiveness of ledipasvir/sofosbuvir (LDV/SOF) in treatment-experienced cirrhotic genotype 1 patients with chronic hepatitis C: a comparative analysis of Gilead sponsored trials with 4 real-world cohorts. J Hepatol 2016;64:S797.
[45] Vermehren J, Maasoumy B, Maan R, Cloherty G, Berkowski C, Feld JJ, et al. Applicability of hepatitis C virus RNA viral load thresholds for 8-week treatments in patients with chronic hepatitis C virus genotype 1 infection. Clin Infect Dis 2016;62:1228–1234.
[46] Townsend KS, Osinusi A, Nelson AK, Kohli A, Gross C, Polis MA, et al. High efficacy of sofosbuvir/ledipasvir for the treatment of HCV genotype 1 in patients coinfected with HIV on and off antiretroviral therapy: results from the NIAID ERADICATE trial. Hepatology 2014;60:240A–241A.
[47] Bourlière M, Sulkowski MS, Omata M, Zeuzem S, Feld JJ, Lawitz E, et al. An integrated safety and efficacy analysis of >500 patients with compensated cirrhosis treated with ledipasvir/sofosbuvir with or without ribavirin. Hepatology 2014;60:239A.
[48] Bourlière M, Bronowicki JP, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, et al. Ledipasvir/sofosbuvir fixed dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy. Hepatology 2014;60:1271A.
[49] Zeuzem S, Mizokami M, Pianko S, Mangia A, Han KH, Martin R, et al. Prevalence of pretreatment NS5A resistance associated variants in genotype 1 patients across different regions using deep sequencing and effect on treatment outcome with LDV/SOF. Hepatology 2015;62:254A.
[50] Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol 2016;64:486–504.
[51] Feld JJ, Jacobson IM, Hezode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373:2599–2607.
[52] Wyles D, Brau N, Kottilil S, Daar E, Workowski K, Luetkemeyer A, et al. Sofosbuvir/velpatasvir fixed dose combination for 12 weeks in patients coinfected with HCV and HIV-1: the Phase 3 ASTRAL-5 study. J Hepatol 2016;64:S188–S189.
[53] Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1594–1603.
[54] Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med 2014;370:1983–1992.
[55] Dore GJ, Conway B, Luo Y, Janczewska E, Knysz B, Liu Y, et al. Efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir compared to IFN-containing regimens in genotype 1 HCV patients: The MALACHITE-I/II trials. J Hepatol 2016;64:19–28.
[56] Wyles DL, Sulkowski MS, Eron JJ, Trinh R, Lalezari J, Slim J, et al. TURQUOISE-I: 94% SVR12 in HCV/HIV-1 coinfected patients treated with ABT-450/r/ombitasvir, dasabuvir and ribavirin. Hepatology 2014;60:1136A–1137A.
[57] Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourliere M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med 2014;370:1604–1614.
[58] Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147:359–365 e351.
[59] Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014;370:1973–1982.
[60] Feld JJ, Moreno C, Trinh R, Tam E, Bourgeois S, Horsmans Y, et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12weeks. J Hepatol 2016;64:301–307.
[61] Rockstroh JK, Nelson M, Katlama C, Lalezari J, Mallolas J, Bloch M, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV 2015;2:e319–e327.
[62] Zeuzem S, Rockstroh J, Kwo PY, Roth D, Lawitz E, Sulkowski MS, et al. Predictors of response to grazoprevir/elbasvir among HCV genotype 1 (GT1)-infected patients: integrated analysis of Phase 2–3 trials. Hepatology 2015;62:554A–555A.
[63] Kwo P, Gane E, Peng CY, Pearlman B, Vierling JM, Serfaty L, et al. Efficacy and safety of grazoprevir/elbasvir plus or minus RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-EDGE Treatment-Experienced trial. J Hepatol 2015;62:S674–S675.
[64] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211–221.
[65] Luetkemeyer AF, McDonald C, Ramgopal M, Noviello S, Bhore R, Ackerman P. 12 weeks of daclatasvir in combination with sofosbuvir for HIV-HCV coinfection (ALLY-2 study): efficacy and safety by HIV combination antiretroviral regimens. Clin Infect Dis 2016;62:1489–1496.
[66] Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology 2016;63:1493–1505.
[67] Foster GR, Afdhal N, Roberts SK, Brau N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015;373:2608–2617.
[68] Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-Oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 Phase 3 Study. Hepatology 2015;61:1127–1135.
[69] Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). Hepatology 2016;63:1430–1441.
[70] Kapoor R, Kohli A, Sidharthan S, Sims Z, Petersen TL, Osinusi A, et al. All-oral treatment for genotype 4 chronic hepatitis C infection with sofosbuvir and ledipasvir: interim results from the NIAID SYNERGY trial. Hepatology 2014;60:321A.
[71] Abergel A, Metivier S, Samuel D, Jiang D, Kersey K, Pang PS, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology 2016, [Epub ahead of print].
[72] Pol S, Reddy KR, Baykal T, Hezode C, Hassanein T, Marcellin P, et al. Interferon-free regimens of ombitasvir and ABT-450/r with or without ribavirin in patients with HCV genotype 4 infection: PEARL-I study results. Hepatology 2014;60:1129A.
[73] Asselah T, Hezode C, Qaqish RB, Elkhasbab M, Hassanein T, Papatheodoridis GV, et al. High SVR rates in patients with genotype 4 chronic hepatitis C infection and compensated cirrhosis with ombitasvir/paritaprevir/ritonavir co-administered with ribavirin (AGATE-I). J Hepatol 2016;64:S827.
[74] Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med 2015;163:1–13.
[75] Buti M, Calleja JL, Forns X, Diago M, Ortega E, Crespo J, et al. Simeprevir plus sofosbuvir for hepatitis C virus genotype 4 infection: a Phase III open-label study. J Hepatol 2016;64:S220–S221.
[76] Abergel A, Asselah T, Metivier S, Kersey K, Jiang D, Mo H, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis 2016;16:459–464.
[77] Gane EJ, Hyland RH, An D, Svarovskaia ES, Pang PS, Symonds WT, et al. High efficacy of LDV/SOF regimens for 12 weeks for patients with HCV genotype 3 or 6 infection. Hepatology 2014;60:1274A.
[78] Garcia-Retortillo M, Forns X, Feliu A, Moitinho E, Costa J, Navasa M, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatology 2002;35:680–687.
[79] Gane E, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. Transplantation 2002;74:427–437.
[80] Flamm SL, Everson GT, Charlton M, Denning JM, Arterburn S, Brandt-Sarif T, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of HCV in patients with decompensated cirrhosis: preliminary results of a prospective, multicenter study. Hepatology 2014;60:320A.
[81] Curry MP, Forns X, Chung RT, Terrault NA, Brown Jr R, Fenkel JM, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100–107 e101.
[82] Zuckerman E, Ashkenazi E, Kovalev Y, Weitsman E, Kaspa RT, Brown M, et al. The real-world Israeli experience of treating chronic hepatitis C, genotype 1 patients with advanced fibrosis with paritaprevir/ritonavir/ombitasvir, dasabuvir with or without ribavirin: a large multi-center cohort. J Hepatol 2016;64:S137.
[83] Flisiak R, Jaroszewicz J, Janczewska E, Wawrzynowicz-Syczewska M, Grabinska A, Bolewska B, et al. Predictors of hepatic decompensation during ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin treatment

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

of genotype 1 and 4 HCV infected patients (real-life AMBER study). J Hepatol 2016;64:S815.
[84] Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown Jr RS, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649–659.
[85] Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, Buti M, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16:685–697.
[86] Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–2628.
[87] Foster GR, Irving WL, Cheung MC, Walker AJ, Hudson BE, Verma S, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224–1231.
[88] Cheung MC, Walker AJ, Hudson BE, Verma S, McLauchlan J, Mutimer DJ, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016, [Epub ahead of print].
[89] Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub SR, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. J Hepatol 2016;65:524–531.
[90] Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology 2002;122:889–896.
[91] Prieto M, Berenguer M, Rayon JM, Cordoba J, Arguello L, Carrasco D, et al. High incidence of allograft cirrhosis in hepatitis C virus genotype 1b infection following transplantation: relationship with rejection episodes. Hepatology 1999;29:250–256.
[92] Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilabert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. Hepatology 2006;43:492–499.
[93] Neumann UP, Berg T, Bahra M, Seehofer D, Langrehr JM, Neuhaus R, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. J Hepatol 2004;41:830–836.
[94] Charlton M, Gane E, Manns MP, Brown Jr RS, Curry MP, Kwo PY, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015;148:108–117.
[95] Forns X, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C following liver transplantation. Hepatology 2015;61:1485–1494.
[96] Flamm S, Bacon B, Curry M, Dieterich D, Guest L, Kowdley KV, et al. Ledipasvir/sofosbuvir ± ribavirin in HCV post-transplant patients: real-world heterogeneous population from the TRIO network. J Hepatol 2016;64: S822.
[97] Ciesek S, Proske V, Otto B, Pischke S, Costa R, Luthgehetmann M, et al. Efficacy and safety of sofosbuvir/ledipasvir for the treatment of patients with hepatitis C virus re-infection after liver transplantation. Transplant Infect Dis 2016;18:326–332.
[98] Coilly A, Fougerou-Leurent C, de Ledinghen V, Houssel-Debry P, Duvoux C, Di Martino V, et al. Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence – The ANRS CUPILT study. J Hepatol 2016, [Epub ahead of print].
[99] Mantry PS, Kwo PY, Coakley E, Te HS, Vargas HE, Brown RS, et al. High sustained virologic response rates in liver transplant recipients with recurrent HCV genotype 1 infection receiving ABT-450/r/ombitasvir plus dasabuvir plus ribavirin. Hepatology 2014;60:298A–299A.
[100] Coilly A, Pageaux GP, Houssel-Debry P, Duvoux C, Radenne S, De Ledinghen V, et al. Improving liver function and delisting of patients awaiting liver transplantation for HCV cirrhosis: do we ask too much to DAAs? Hepatology 2015;62:257A.
[101] Fernandez-Carrillo C, Lens S, Llop E, Pascasio JM, Fernandez I, Baliellas C, et al. Treatment of hepatitis C virus in patients with advanced cirrhosis: always justified? Analysis of the HEPA-C registry. J Hepatol 2016;64: S133.
[102] Moon C, Jung KS, Kim DY, Baatarkhuu O, Park JY, Kim BK, et al. Lower incidence of hepatocellular carcinoma and cirrhosis in hepatitis C patients with sustained virological response by pegylated interferon and ribavirin. Dig Dis Sci 2015;60:573–581.
[103] Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013;158:329–337.
[104] Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct acting antivirals. J Hepatol 2016, [Epub ahead of print].
[105] Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol 2016, [Epub ahead of print].
[106] Camma C, Cabibbo G, Craxi A. Direct antiviral agents and risk for HCC early recurrence: much ado about nothing. J Hepatol 2016, [Epub ahead of print].
[107] ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CIRVIR and CO23 CUPILT cohorts). Lack of evidence of an effect of direct acting antivirals on the recurrence of hepatocellular carcinoma. J Hepatol 2016, epub ahead of print.
[108] Nault JC, Colombo M. Hepatocellular carcinoma and direct acting antiviral treatments: controversy after the revolution. J Hepatol 2016, [Epub ahead of print].
[109] Potthoff A, Berg T, Wedemeyer H. Late hepatitis B virus relapse in patients co-infected with hepatitis B virus and hepatitis C virus after antiviral treatment with pegylated interferon alpha-2b and ribavirin. Scand J Gastroenterol 2009;44:1487–1490.
[110] Saadoun D, Thibault V, Si Ahmed SN, Alric L, Mallet M, Guillaud C, et al. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. Ann Rheum Dis 2016, [Epub ahead of print].
[111] Sise ME, Bloom AK, Wisocky J, Lin MV, Gustafson JL, Lundquist AL, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology 2016;63:408–417.
[112] Lim LY, La D, Cserti-Gazdewich CM, Shah H. Lymphoma remission by interferon-free HCV eradication without chemotherapy. ACG Case Rep J 2015;3:69–70.
[113] Sultanik P, Klotz C, Brault P, Pol S, Mallet V. Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment. Blood 2015;125:2446–2447.
[114] Saxena V, Koraishy FM, Sise ME, Lim JK, Schmidt M, Chung RT, et al. Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. Liver Int 2016;36:807–816.
[115] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002798/WC500160597.pdf.
[116] Desnoyer A, Pospai D, Le MP, Gervais A, Heurgue-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol 2016;65:40–47.
[117] Bhamidimarri KR, Czul F, Peyton A, Levy C, Hernandez M, Jeffers L, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease. J Hepatol 2015;63:763–765.
[118] Bhamidimarri KR, Martin P. Finally, safe and effective treatment options for hepatitis C in hemodialysis patients. J Hepatol 2016;65:7–10.
[119] Hundemer GL, Sise ME, Wisocky J, Ufere N, Friedman LS, Corey KE, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. Infect Dis (Lond) 2015;47:924–929.
[120] Perumpail RB, Wong RJ, Ha LD, Pham EA, Wang U, Luong H, et al. Sofosbuvir and simeprevir combination therapy in the setting of liver transplantation and hemodialysis. Transplant Infect Dis 2015;17:275–278.
[121] Wanchoo R, Thakkar J, Schwartz D, Jhaveri KD. Harvoni (ledipasvir with sofosbuvir)-induced renal injury. Am J Gastroenterol 2016;111:148–149.
[122] Pockros PJ, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. Gastroenterology 2016;150:1590–1598.
[123] Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour Jr H, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015;386:1537–1545.
[124] Beinhardt S, Al Zoairy R, Ferenci P, Kozbial K, Freissmuth C, Stern R, et al. DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and post-kidney transplantation setting. Transplant Int 2016, [Epub ahead of print].
[125] Kamar N, Marion O, Rostaing L, Cointault O, Ribes D, Lavayssiere L, et al. Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

virus infection after kidney transplantation. Am J Transplant 2016;16:1474–1479.
[126] Lin MV, Sise ME, Pavlakis M, Amundsen BM, Chute D, Rutherford AE, et al. Efficacy and safety of direct acting antivirals in kidney transplant recipients with chronic hepatitis C virus infection. PLoS One 2016;11 e0158431.
[127] Colombo M, Aghemo A, Liu L, Zhang J, Dvory-Sobol H, Hyland RH, et al. Treatment with ledipasvir-sofosbuvir for 12 or 24 weeks in kidney transplant recipients with chronic genotype 1 or 4 HCV infection: a randomized trial. J Ann Intern Med 2016, [In revision].
[128] Scott DR, Wong JK, Spicer TS, Dent H, Mensah FK, McDonald S, et al. Adverse impact of hepatitis C virus infection on renal replacement therapy and renal transplant patients in Australia and New Zealand. Transplantation 2010;90:1165–1171.
[129] Van Wagner LB, Baker T, Ahya SN, Norvell JP, Wang E, Levitsky J. Outcomes of patients with hepatitis C undergoing simultaneous liver-kidney transplantation. J Hepatol 2009;51:874–880.
[130] D'Ambrosio R, Aghemo A, Rossetti V, Carrinola R, Colombo M. Sofosbuvir-based regimens for the treatment of hepatitis C virus in patients who underwent lung transplant: case series and review of the literature. Liver Int 2016, [Epub ahead of print].
[131] Darke S, Kaye S, Duflou J. Comparative cardiac pathology among deaths due to cocaine toxicity, opioid toxicity and non-drug-related causes. Addiction 2006;101:1771–1777.
[132] Grebely J, Raffa JD, Lai C, Kerr T, Fischer B, Krajden M, et al. Impact of hepatitis C virus infection on all-cause and liver-related mortality in a large community-based cohort of inner city residents. J Viral Hepat 2011;18:32–41.
[133] Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. Am J Epidemiol 2008;168:1099–1109.
[134] Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011;378:571–583.
[135] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–567.
[136] Grebely J, Robaeys G, Bruggmann P, Aghemo A, Backmund M, Bruneau J, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Int J Drug Policy 2015;26:1028–1038.
[137] Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. J Hepatol 2011;54:1137–1144.
[138] Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. Hepatology 2012;55:49–57.
[139] Harris RJ, Martin NK, Rand E, Mandal S, Mutimer D, Vickerman P, et al. New treatments for hepatitis C virus (HCV): scope for preventing liver disease and HCV transmission in England. J Viral Hepat 2016;23:631–643.
[140] Lalezari J, Sullivan JG, Varunok P, Galen E, Kowdley KV, Rustgi V, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol 2015;63:364–369.
[141] Dore G, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. C-EDGE CO-STAR: efficacy of grazoprevir and elbasvir in persons who inject drugs (PWID) receiving opioid agonist therapy. Hepatology 2015;62:227A–228A.
[142] Smolders EJ, de Kanter CT, de Knegt RJ, van der Valk M, Drenth JP, Burger DM. Drug-drug interactions between direct-acting antivirals and psychoactive medications. Clin Pharmacokinet 2016, [Epub ahead of print].
[143] Lai ME, Origa R, Danjou F, Leoni GB, Vacquer S, Anni F, et al. Natural history of hepatitis C in thalassemia major: a long-term prospective study. Eur J Haematol 2013;90:501–507.
[144] Hezode C, Colombo M, Spengler U, Ben-Ari Z, Strasser S, Lee WM, et al. C-EDGE IBLD: efficacy and safety of elbasvir/grazoprevir (EBR/GZR) in subjects with chronic hepatitis C virus infection and inherited blood disorders. J Hepatol 2016;64:S753.
[145] Chevaliez S, Bouvier-Alias M, Brillet R, Pawlotsky JM. Overestimation and underestimation of hepatitis C virus RNA levels in a widely used real-time polymerase chain reaction-based method. Hepatology 2007;46:22–31.
[146] Sarrazin C, Shiffman ML, Hadziyannis SJ, Lin A, Colucci G, Ishida H, et al. Definition of rapid virologic response with a highly sensitive real-time PCR-based HCV RNA assay in peginterferon alfa-2a plus ribavirin response-guided therapy. J Hepatol 2010;52:832–838.
[147] Vermehren J, Kau A, Gartner BC, Gobel R, Zeuzem S, Sarrazin C. Differences between two real-time PCR-based hepatitis C virus (HCV) assays (RealTime HCV and Cobas AmpliPrep/Cobas TaqMan) and one signal amplification assay (Versant HCV RNA 3.0) for RNA detection and quantification. J Clin Microbiol 2008;46:3880–3891.
[148] Renard S, Borentain P, Salaun E, Benhaourech S, Maille B, Darque A, et al. Severe pulmonary arterial hypertension in patients treated for hepatitis C with sofosbuvir. Chest 2016;149:e69–e73.
[149] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales Jr FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975–982.
[150] Hadziyannis SJ, Sette Jr H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004;140:346–355.
[151] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958–965.
[152] Fried MW. Side effects of therapy of hepatitis C and their management. Hepatology 2002;36:S237–S244.
[153] Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology 2007;46:371–379.
[154] Soza A, Everhart JE, Ghany MG, Doo E, Heller T, Promrat K, et al. Neutropenia during combination therapy of interferon alfa and ribavirin for chronic hepatitis C. Hepatology 2002;36:1273–1279.
[155] Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, et al. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology 2004;126:1302–1311.
[156] Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, et al. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. Hepatology 2004;40:1450–1458.
[157] Sulkowski MS, Poordad F, Manns MP, Bronowicki JP, Rajender Reddy K, Harrison SA, et al. Anemia during treatment with peginterferon alfa-2b/ribavirin and boceprevir: analysis from the serine protease inhibitor therapy 2 (SPRINT-2) trial. Hepatology 2013;57:974–984.
[158] Alavian SM, Aalaei-Andabili SH. Education by a nurse increases the adherence to therapy in chronic hepatitis C patients. Clin Gastroenterol Hepatol 2012;10:203.
[159] Rodis JL, Kibbe P. Evaluation of medication adherence and quality of life in patients with hepatitis C virus receiving combination therapy. Gastroenterol Nurs 2010;33:368–373.
[160] Alexander JA, Hearld LR, Mittler JN, Harvey J. Patient-physician role relationships and patient activation among individuals with chronic illness. Health Serv Res 2012;47:1201–1223.
[161] Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. Gastroenterology 2006;130:1607–1616.
[162] Bruggmann P, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. Drug Alcohol Depend 2010;110:167–171.
[163] Le Lan C, Guillygomarc'h A, Danielou H, Le Dreau G, Laine F, Vedeilhie C, et al. A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. J Hepatol 2012;56:334–340.
[164] Siu L, Foont J, Wands JR. Hepatitis C virus and alcohol. Semin Liv Dis 2009;29:188–199.
[165] Backmund M, Meyer K, Edlin BR. Infrequent reinfection after successful treatment for hepatitis C virus infection in injection drug users. Clin Infect Dis 2004;39:1540–1543.
[166] Currie SL, Ryan JC, Tracy D, Wright TL, George S, McQuaid R, et al. A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus. Drug Alcohol Depend 2008;93:148–154.
[167] Dalgard O. Follow-up studies of treatment for hepatitis C virus infection among injection drug users. Clin Infect Dis 2005;40:S336–S338.
[168] Grebely J, Knight E, Ngai T, Genoway KA, Raffa JD, Storms M, et al. Reinfection with hepatitis C virus following sustained virological response in injection drug users. J Gastroenterol Hepatol 2010;25:1281–1284.
[169] Grebely J, Pham ST, Matthews GV, Petoumenos K, Bull RA, Yeung B, et al. Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. Hepatology 2012;55:1058–1069.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

Guidelines

[170] Martin TC, Ingiliz P, Rodger A, Stellbrink HJ, Mauss S, Boesecke C, et al. HCV reinfection incidence and outcomes among HIV infected MSM in Western Europe. J Hepatol 2016;64:S138.

[171] Wyles DL, Pockros PJ, Yang JC, Zhu Y, Pang PS, McHutchison JG, et al. Retreatment of patients who failed prior sofosbuvir-based regimens with all-oral fixed-dose combination ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Hepatology 2014;60:317A.

[172] Hezode C, Chevaliez S, Scoazec G, Soulier A, Varaut A, Bouvier-Alias M, et al. Retreatment with sofosbuvir and simeprevir of patients with hepatitis C virus genotype 1 or 4 who previously failed a daclatasvir-containing regimen. Hepatology 2016;63:1809–1816.

[173] Hezode C, Fourati S, Scoazec G, Soulier A, Varaut A, Francois M, et al. Retreatment of HCV DAA failures: HCV infection may be incurable. J Hepatol 2016;64:S400.

[174] Gane EJ, Shiffman M, Etzkorn K, Morelli G, Stedman C, Davis MN, et al. Sofosbuvir/velpatasvir in combination with ribavirin for 24 weeks is effective retreatment for patients who failed prior NS5A-containing DAA regimens: results of the retreatment study. J Hepatol 2016;64:S147.

[175] Poordad F, Bennett M, Sepe TE, Cohen E, Reindollar RW, Everson G, et al. Ombitasvir/paritaprevir/r, dasabuvir and sofosbuvir treatment of patients with genotype 1 infection who failed a prior course of DAA therapy: the QUARTZ-I study. J Hepatol 2016;64:S767–S768.

[176] Vermehren J, Susser S, Dietz J, von Hahn T, Petersen J, Hinrichsen H, et al. Retreatment of patients who failed DAA-combination therapies: real-world experience from a large hepatitis C resistance database. J Hepatol 2016;64:S188.

[177] Camma C, Almasio P, Craxi A. Interferon as treatment for acute hepatitis C. A meta-analysis. Dig Dis Sci 1996;41:1248–1255.

[178] Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology 2003;125:80–88.

[179] Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34–41.

[180] Poynard T, Regimbeau C, Myers RP, Thevenot T, Leroy V, Mathurin P, et al. Interferon for acute hepatitis C. Cochrane Database Syst Rev 2002;1 CD000369.

[181] Basu PP, Shah NJ, Aloysius MM, Brown Jr R. Sofosbuvir and ledipasvir *vs.* sofosbuvir and simeprevir for acute hepatitis C: a RCT (SLAM C study). Hepatol Int 2016;10:S14–S15.

[182] Rockstroh JK, Bhagani S, Hyland RH, Yun C, Zheng W, Brainard D, et al. Ledipasvir/sofosbuvir for 6 weeks in HIV-infected patients with acute HCV infection. Conference on Retroviruses and Opportunistic Infections (CROI), February 22–25, Boston, Massachusetts.

[183] Deterding K, Spinner C, Schott E, Welzel T, Gerken G, Klinker H, et al. Six weeks of sofosbuvir/ledipasvir (SOF/LDV) are sufficient to treat acute hepatitis C virus genotype 1 monoinfection: the HEPNET acute HCV IV study. J Hepatol 2016;64:S211.

Please cite this article in press as: , . EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001