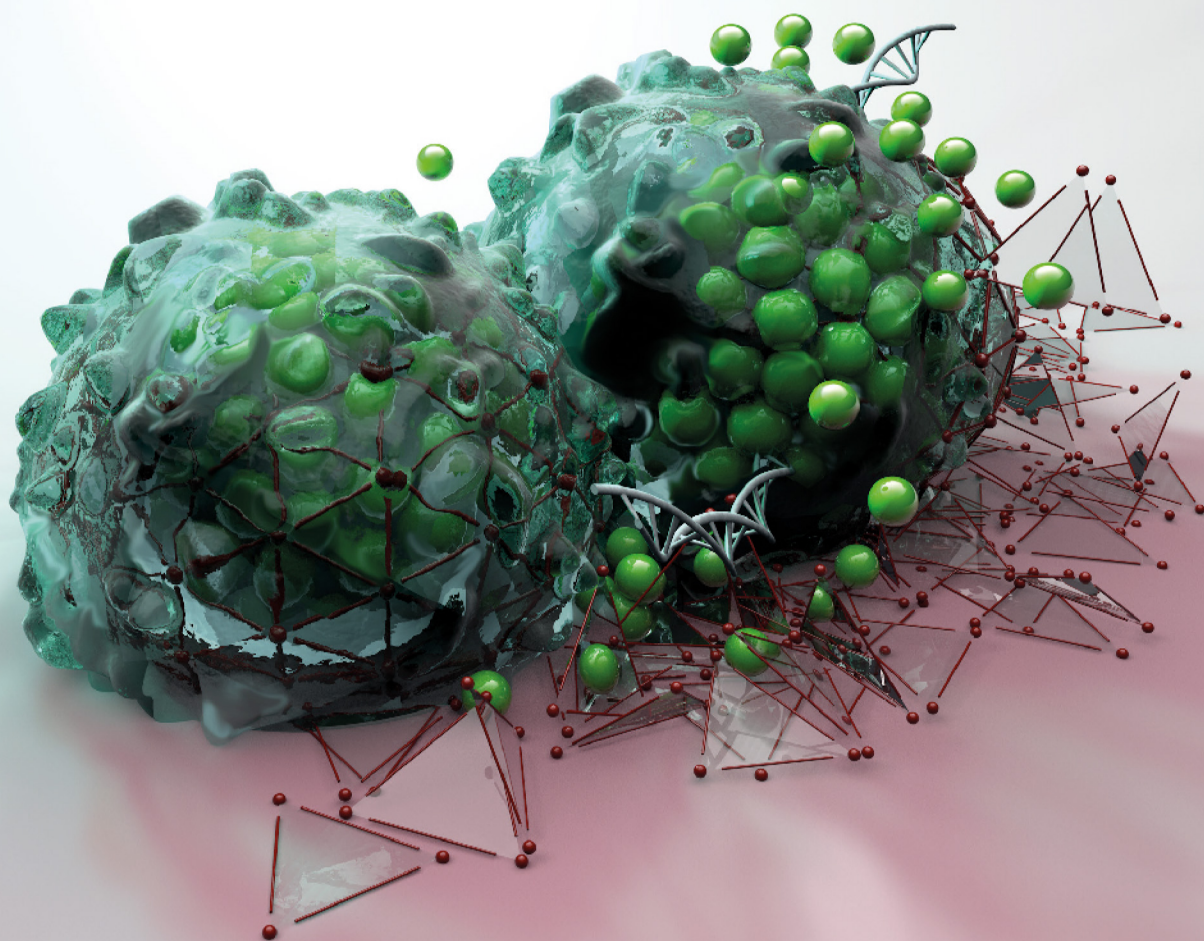


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EASL Recommendations on Treatment of Hepatitis C

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EASL

European Association
for the Study of the Liver

Coordinator: Jean-Michel Pawlotsky
Panel members: Alessio Aghemo (EASL Governing Board)
Geoffrey Dusheiko
Xavier Forns
Massimo Puoti
Christophe Sarrazin

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EASL Office

7 rue Daubin, 1203 Geneva, Switzerland
 Tel: (+41) 22 807 03 67
 Fax: (+41) 22 510 24 00
 e-mail: easloffice@easloffice.eu

Coordinator: Jean-Michel Pawlotsky
 Panel members: Alessio Aghemo (EASL governing Board)
 Geoffrey Dusheiko
 Xavier Forns
 Massimo Puoti
 Christophe Sarrazin

1. Introduction

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

These EASL Recommendations on Treatment of Hepatitis C are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, in the clinical decision-making process by describing the optimal management of patients with acute and chronic HCV infections. These guidelines apply to therapies that will be approved within less than 6 months at the time of their publication.

2. The standard of care up to 2014

The primary goal of HCV therapy is to cure the infection. A sustained virological response (SVR) is defined as undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after treatment completion. The infection is cured in more than 99% of patients who achieve an SVR. The SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. More data is required to ascertain the lifetime residual risk of hepatocellular carcinoma after viral infection has been eradicated.

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

In 2011, telaprevir and boceprevir were licensed for use in HCV genotype 1 infection. These two drugs are first-wave, first-generation direct-acting antivirals (DAAs). Both target the HCV NS3/4A serine protease and are thus referred to as protease inhibitors. Both telaprevir and boceprevir must be administered in combination with pegylated IFN- α and ribavirin. In the phase III trials of boceprevir and telaprevir in HCV genotype 1 treatment-naïve patients, triple therapy regimens achieved higher SVR rates than pegylated IFN- α /ribavirin dual therapy, of the order of 65% to 75% [4-7]. However, the side effect profiles of these triple combination therapies are not favourable, and the costs per SVR in patients with advanced hepatic fibrosis are such that they should ideally no longer be used in patients infected with HCV genotype 1, as soon as other, more efficacious and better-tolerated options are available.

In addition to pegylated IFN- α and ribavirin, three new HCV DAAs will be licenced in the EU in the first half of 2014, for use as part of combination therapies for HCV infection. Sofosbuvir, a nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase, has been approved in January 2014. Simeprevir, a second-wave, first-generation NS3/4A protease inhibitor will be approved in May 2014. Daclatasvir, an NS5A inhibitor, is likely to be approved in August or September 2014. Other drugs may be approved later in 2014 or in 2015 and an update of these guidelines will be provided when this is the case.

The panel recognises the heterogeneity of per capita incomes and health insurance systems across Europe and in other regions, and therefore the possible necessity to continue to utilise current standards of care with pegylated IFN- α and ribavirin, with or without the first-generation protease inhibitors telaprevir or boceprevir. However the advent of new DAAs implies that these regimens are not considered optimal in 2014. 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.

3. Methodology

These EASL Recommendations have been updated 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. Where possible, the level of evidence and recommendation are cited. The evidence and recommendations in these guidelines 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 [26]. The quality of the evidence in the CPG 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 CPGs 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 licenced drugs. Several major Phase III trials have been completed and filing for licencing has been completed or is imminent. The panel could not recommend treatments with these compounds, but provides a perspective at the end, given the likely importance of these imminent regimens under review. These Recommendations will be updated regularly, following approval of new drug regimens by the European Medicines Agency.

4. Recommendations

4.1. Diagnosis of acute and chronic hepatitis C

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

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

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

aminotransferase [ALT] >10 times the upper limit of normal, jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, and/or if a likely recent source of transmission is identifiable. In all cases, HCV RNA can be detected during the acute phase although brief periods of undetectable HCV RNA may occur.

The diagnosis of chronic hepatitis C is based on the detection of both HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis, either by elevated aminotransferases or by histological changes of chronic hepatitis C. Since, in the case of a newly acquired HCV infection, spontaneous viral clearance is very rare beyond four to six months of infection, the diagnosis of chronic hepatitis C can be made after that time period.

Recommendations

Recommendations

- Anti-HCV antibodies are the first line diagnostic test for HCV infection (**Recommendation A1**)
- In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation (**Recommendation A1**)
- If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method (**Recommendation A1**)
- Anti-HCV positive, HCV-RNA negative individuals should be retested for HCV RNA 3 months later to confirm true convalescence (**Recommendation A1**)

4.2. Goals and endpoints of HCV therapy

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

The endpoint of therapy is an SVR, defined by undetectable HCV RNA 12 weeks (SVR12) or 24 weeks (SVR24) after the end of therapy, as assessed by a sensitive molecular method with a lower limit of detection <15 IU/ml. Both SVR12 and SVR24 have been accepted as endpoints of therapy by regulators in the US and Europe, given that their concordance is 99% [10]. Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases [11].

Recommendations

Recommendations

- The goal of therapy is to eradicate HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, and death. The endpoint of therapy is undetectable HCV RNA in a sensitive assay (<15 IU/ml) 12 and 24 weeks after the end of treatment (i.e. an SVR) (**Recommendation A1**)
- In patients with 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 (**Recommendation A1**)

4.3. Pre-therapeutic assessment

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

4.3.1. Search for other causes of liver disease

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

4.3.2. 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 post-treatment prognosis depends on the stage of fibrosis. The absence of significant fibrosis may also have important implications for stratification of disease and possibly the timing of therapy.

Assessment of the stage of fibrosis is not required in patients with clinical evidence of cirrhosis. Patients with cirrhosis need surveillance for HCC. Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT patterns.

Liver biopsy remains the reference method for grading the activity and histological progression (staging) of the disease. The risk of severe complications of liver biopsy is very low (1/4,000-10,000). In chronic hepatitis C, considerable evidence suggest that non-invasive methods can now be used instead of liver biopsy to assess liver disease severity prior to therapy at a safe level of predictability. Liver stiffness measurement (LSM) can be used to assess liver fibrosis in patients with chronic hepatitis C, provided that consideration is given to factors that may adversely affect its performance such as obesity. Well-established panels of biomarkers of fibrosis can also be applied. Both LSM and biomarkers perform well in the identification of cirrhosis or no fibrosis, but they perform less well in resolving intermediate degrees of fibrosis.

The combination of blood biomarkers or the combination of LSM and a blood test improve accuracy and reduce the need for liver biopsy to resolve uncertainty [12, 13]. These tests are of particular interest in patients with coagulation disorders, though transjugular liver biopsy may also be used safely in this situation with the bonus that portal pressure can also be assessed. In case of contradictory results with non-invasive markers, liver biopsy may be indicated. Also, histology may be required in cases of known or suspected mixed aetiologies (e.g., HCV infection with HBV infection, metabolic syndrome, alcoholism or autoimmunity).

4.3.3. HCV RNA level and genotype determination

HCV RNA quantification is indicated for the patient who may undergo antiviral treatment. HCV quantification should be made by a reliable sensitive assay, and levels should be expressed in IU/ml. The HCV genotype should also be assessed prior to treatment initiation. Genotype 1 subtyping (1a/1b) provides relevant information with respect to different response rates, genetic barriers to resistance, and treatment modalities. Genotyping/subtyping should be performed with an assay that discriminates well subtypes 1a and 1b [14].

4.3.4. Determination of host genetics

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

Recommendations

Recommendations

- The causal relationship between HCV infection and liver disease should be established (**Recommendation A1**)
- The contribution of co-morbid conditions to the progression of liver disease must be evaluated and appropriate corrective measures implemented (**Recommendation A1**)
- Liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted (**Recommendation 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 (**Recommendation A1**)
- HCV RNA detection and quantification should be made by a sensitive assay (lower limit of detection of <15 IU/ml) (**Recommendation A1**)
- The HCV genotype and genotype 1 subtype (1a/1b) must be assessed prior to treatment initiation and will determine the choice of therapy (**Recommendation A1**)
- *IL28B* genotyping has no role in the indication for treating hepatitis C with the new DAAs (**Recommendation A1**)

4.4. Contra-indications to therapy

4.4.1. IFN- α and ribavirin

Treatment of chronic hepatitis C with pegylated IFN- α /ribavirin-containing regimens is absolutely contra-indicated in the following patient groups: uncontrolled depression, psychosis or epilepsy; pregnant women or couples unwilling to comply with adequate contraception; severe concurrent medical diseases and comorbidities including retinal disease, autoimmune thyroid disease; decompensated liver disease. The use of pegylated IFN- α is not recommended in patients with absolute neutrophil counts <1500/mm³ and/or platelet counts $\leq$ 90,000/mm³. Treatment of patients with advanced liver disease whose parameters fall outside of label recommendations may be feasible in experienced centres under careful monitoring and informed consent.

4.4.2. Approved DAAs

Based on existing knowledge, no absolute contra-indications to the DAAs in the EU region in 2014 exist.

4.5. Indications for treatment: Who should be treated?

All treatment-naïve and -experienced patients with compensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy. Treatment should be prioritized in patients with advanced fibrosis (METAVIR score F3 to F4) and in those patients with clinically significant extra-hepatic manifestations (symptomatic cryoglobulinaemia or HCV immune complex nephropathy). Treatment is justified in patients with moderate fibrosis (METAVIR score F2). For patients with minimal or no fibrosis (METAVIR score F0-F1), the timing

and nature of therapy is debatable, and treatment may be deferred. The decision to defer treatment for a specific patient should consider the patient's preference and priorities, the natural history and risk of progression, the presence of co-morbidities including HIV coinfection, and the patient's age. Patients who have treatment deferred should be assessed on a regular basis for evidence of progression, to reconsider the indication for treatment, and to discuss new therapies as they emerge.

IFN-free, ideally ribavirin-free therapy may also be considered in patients with decompensated cirrhosis. Although scarce data is available in that population, these patients are those who may benefit more from HCV eradication in the short-term. IFN-free treatment in patients with decompensated disease should only be attempted in experienced centers until further safety and efficacy data have accumulated.

Recommendations

Recommendations

- All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy (**Recommendation A1**)
- Treatment should be prioritized for patients with significant fibrosis (METAVIR score F3 to F4) (**Recommendation A1**)
- Treatment is justified in patients with moderate fibrosis (METAVIR score F2) (**Recommendation A2**)
- In patients with no or mild disease (METAVIR score F0-F1), the indication for and timing of therapy can be individualized (**Recommendation B1**)
- Patients with decompensated cirrhosis who are on the transplant list should be considered for IFN-free, ideally ribavirin-free therapy (**Recommendation A1**)

4.6. Available drugs (approved by EMA before the end of 2014)

Pegylated IFN-α2a should be used at the dose of 180 µg/week, whereas **pegylated IFN-α2b** should be used at the weight-based dose of 1.5 µg/kg/week. **Ribavirin** dose should be 1000 or 1200 mg/day, based on body weight (<75 kg or ≥75 kg, respectively).

Sofosbuvir should be administered at the dose of 400 mg (one tablet) once per day. Currently, no dose recommendation can be given for patients with severe renal impairment (estimated glomerular filtration rate <30 ml/min/1.73m²) or with end-stage renal disease due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite.

Sofosbuvir is well tolerated over 12 to 24 weeks of administration. The most common adverse events (≥20%) observed in combination with ribavirin were fatigue and headache. The most common adverse events (≥20%) observed in combination with pegylated IFN-α and ribavirin were fatigue, headache, nausea, insomnia, and anaemia.

Drugs that are potent P-gp inducers significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect. Thus sofosbuvir should not be administered with other known inducers of P-gp, such as rifampin, carbamazepine, phenytoin or St. John's wort. No other significant drug-drug interactions have been reported, in particular with all of the antiretroviral agents tested, including emtricitabine, tenofovir, raltegravir, efavirenz, darunavir/ritonavir, and raltegravir, and there are no potential drug-drug interactions with the remaining antiretrovirals. Sofosbuvir AUC is not significantly changed in patients with mild liver impairment, but it is increased 2.3 fold in those with moderate liver impairment.

Simeprevir should be administered at the dose of 150 mg (one capsule) once per day. No dose recommendation can be given for patients with Child-Pugh Class B or C cirrhosis, due to higher simeprevir exposures (particularly in Child-Pugh C patients) that may be associated with increased frequency of adverse reactions.

Simeprevir is well tolerated. 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 transporters OATP1B1 and MRP2 [15], mild, transient hyperbilirubinaemia not accompanied by changes in other liver parameters was observed in approximately 10% of cases.

Co-administration of simeprevir with substances that are moderate or strong inducers or inhibitors of cytochrome P450 3A (CYP3A) is not recommended as this may lead to significantly lower or higher exposure of simeprevir, respectively. A number of compounds are contra-indicated in patients receiving simeprevir, including anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), antibiotics (erythromycin, clarithromycin, telithromycin, 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, delavirdine, 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 immunosuppressants, such as cyclosporine and tacrolimus, based on studies in healthy volunteers [16].

Daclatasvir should be administered at the dose of 60 mg (one tablet) once per day. It is overall well tolerated. Dose adjustments are not needed in patients with Child B or C disease. The most frequently reported side effects with daclatasvir were fatigue, headache, and nausea.

Little information has been released on daclatasvir drug-drug interactions. Daclatasvir is a substrate of CYP3A4 and a substrate and inhibitor of P-gp. The daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz. No dose adjustment is needed with tenofovir. No information on other antiretroviral drugs is available yet. No dose adjustments are required with cyclosporine or tacrolimus. Total daclatasvir AUC is decreased by 40% and 43% in patients with mild or moderate liver impairment, respectively. However, the unbound pharmacologically active fraction is unchanged, thus dose adjustment is not needed in patients with liver impairment.

4.7. Treatment of chronic hepatitis C

In 2014, treatment-naïve and -experienced patients with compensated disease will benefit from a broad choice of drug combinations. Indications will depend on the HCV genotype/subtype and, eventually, the severity of liver disease, the results of prior therapy or the presence at baseline of detectable, pre-existing amino acid substitutions known to confer resistance to a given DAA. The indications are the same in HCV-monoinfected and HIV-coinfected patients. However, treatment alterations or dose adjustments may be needed in the latter due to drug-drug interactions (see above, drug-drug interactions). Acceptance, tolerance, and contraindications to IFN will be a factor.

For each genotype, the available options will be described, followed by a summary of the data available for the given option.

Recommendations

Recommendations

- Indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection (**Recommendation A1**)
- The same treatment regimens can be used in HIV-co-infected patients as in patients without HIV infection, as the virological results of therapy are identical (**Recommendation A1**)
- The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir (**Recommendation A1**)
- The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz (**Recommendation B2**)
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (**Recommendation A2**)

4.7.1. Treatment of HCV genotype 1 infection

Six treatment options are available for patients infected with HCV genotype 1, including IFN/ribavirin-containing and IFN-free ones. Regardless of the respective costs of these options, the triple combination of pegylated IFN- α , ribavirin, and sofosbuvir (Option 1) appears as the most efficacious and the easiest to use IFN-containing option, without the risk of selecting resistant viruses in case of treatment failure. The combination of sofosbuvir and simeprevir with or without ribavirin (Option 5) and the combination of sofosbuvir and daclatasvir with or without ribavirin (Option 6) appear as the most attractive IFN-free combinations in April 2014. The combination of sofosbuvir and ribavirin (Option 4) is suboptimal in patients infected with HCV genotype 1 and should be reserved to cases for which no other option is available. In settings where none of these options is available, the triple combination of pegylated IFN- α , ribavirin and either telaprevir or boceprevir remains acceptable [17].

Genotype 1, Option 1

Recommendation

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

Comments: This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients [18]. The overall SVR rate was 89% (259/291), 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b. Patients with cirrhosis had a lower SVR rate than non-cirrhotics (80% vs. 92%, respectively). Patients who failed on this regimen did not select HCV variants resistant to sofosbuvir. No data with this regimen has been presented in treatment-experienced patients or in HIV-coinfected patients, and relatively small numbers of patients with cirrhosis were included. Whether longer treatment duration would be needed in the most difficult-to-treat population, i.e., prior non-responders with cirrhosis, is unknown.

Genotype 1, Option 2

Recommendations

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

Comments: This combination has been evaluated in the QUEST-1 and QUEST-2 Phase III clinical trials in treatment-naïve patients [19-21]. The overall SVR rates were 80% (210/264) and 81% (209/257), respectively. In a pooled analysis of both trials, patients infected with subtype 1b achieved an SVR in 85% of cases (228/267). Patients infected with subtype 1a achieved an SVR in 84% of cases (138/165) when no Q80K substitution was detectable in the NS3 protease sequence at baseline. The SVR was 58% only (49/84) when a Q80K substitution was detectable at baseline by population sequencing. SVR was achieved with this regimen in 84% (317/378) of patients with an F0-F2 METAVIR score, 73% (60/82) of patients with F3, and 60% (29/48) of patients with F4 (cirrhosis). However, for patients who received 24 weeks of treatment and had an HCV RNA level <25 IU/ml at week 4, the SVR rate was lower in those with detectable than in those with undetectable HCV RNA at week 4 (69% vs. 93%, respectively) [19-21]. In treatment-naïve, HIV-coinfected patients in the C212 study, SVR was achieved in 79% of patients (42/53).

In mono-infected patients who previously relapsed to IFN- α -ribavirin-based therapy, SVR was achieved in 86% (128/149) of subtype 1b patients and in 70% (78/111) of subtype 1a patients, including 78% in those without and 47% in those with a detectable Q80K substitution at baseline, respectively [22]. In C212, the SVR rate in HIV-coinfected relapsers was 87% (13/15) (Dieterich *et al.*, CROI 2014).

In the ATTAIN Phase III study, SVR was achieved in 69.7% (163/234) of partial responders and 43.6% (63/145) of null responders to IFN- α -ribavirin-based therapy with the triple combination of pegylated IFN- α , ribavirin, and simeprevir, vs. 68.5% (163/238) and 46.6% (67/146) in the same groups receiving telaprevir, respectively (Reddy *et al.*, 2014 Annual Meeting of the Asian-Pacific Association for the Study of the Liver). In the C212 study in HIV-coinfected patients, 70% (7/10) of partial responders and 57% (16/28) of null responders achieved an SVR (Dieterich *et al.*, CROI 2014).

Genotype 1, Option 3

Recommendations

- Patients infected with HCV genotype 1, subtype 1b can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily daclatasvir (60 mg) 24 weeks (**Recommendation B1**)
- This combination should not be proposed to patients infected with HCV genotype 1, subtype 1a, given the preliminary data available, pending results of on-going large-scale studies (**Recommendation B1**)
- Daclatasvir should be administered 12 weeks in combination with pegylated IFN- α and ribavirin. Daclatasvir should be continued in combination with pegylated IFN- α and ribavirin an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10. Pegylated IFN- α and ribavirin should be continued alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 (**Recommendation B2**)

Comments: Although this combination is theoretically effective, few data is available, pending the results of on-going large-scale Phase III studies in the US. The Phase IIb COMMAND-1 study in genotype 1 treatment-naïve patients has shown SVR rates of 87% (27/31) in subtype 1b subjects and 58% only (66/113) in subtype 1a subjects [23].

Genotype 1, Option 4

Recommendations

- Patients infected with HCV genotype 1 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation B2**)
- This combination should be proposed to these patients exclusively when no other IFN-free option is available (**Recommendation B2**)

Comments: This combination is suboptimal in patients infected with HCV genotype 1. In the ELECTRON Phase IIb trial [24], the SVR rates were 84% (21/25) in treatment-naïve patients, but only 10% (1/10) in treatment-experienced patients after 12 weeks of sofosbuvir plus ribavirin. In the SPARE Phase IIb trial in treatment-naïve patients with unfavourable treatment characteristics (majority of males, African Americans, *IL28B* non-CC, high body weight, HCV genotype 1a and 23% cirrhosis) [25], 68% (17/25) of patients receiving weight-based ribavirin and 48% (12/25) of those receiving a low fixed dose of ribavirin achieved an SVR after 24 weeks of therapy. In the QUANTUM study, treatment-naïve patients infected with genotype 1 treated for 12 or 24 weeks achieved SVR rates of 47% to 53% [26]. SVR was achieved in 75% of treatment-naïve and -experienced HIV-coinfected patients (85/114) in the PHOTON-1 Phase III trial [27].

Genotype 1, Option 5

Recommendations

- Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) for 12 weeks (**Recommendation B1**)
- Preliminary results do not indicate a major advantage of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B1**)

Comments: This recommendation is based on preliminary results from the COSMOS Phase IIb trial [28]. In the first cohort, 80 prior null-responders to pegylated IFN- α -ribavirin- therapy with a METAVIR score F0 to F2 were treated 12 or 24 weeks, with or without ribavirin. The SVR rates were 96% (26/27) and 93% (13/14) for 12 weeks of therapy with and without ribavirin, respectively, and 79% (19/24) and 93% (14/15) for 24 weeks of therapy with and without ribavirin, respectively. In the second cohort, 87 treatment-naïve patients and prior null responders with a METAVIR score F3-F4 were treated 12 or 24 weeks, with or without ribavirin. Only SVR rates at week 4 post-treatment are available for this cohort in patients treated for 12 weeks. They were 100% (7/7) and 100% (12/12) with and without ribavirin, respectively, in treatment-naïve patients, and 100% (7/7) and 93% (14/15) with and without ribavirin, respectively, in prior null responders. No patients experienced a virological breakthrough on treatment. All of the 3 patients with virological failure in cohort 1 relapsed and they were infected with HCV subtype 1a and had a detectable Q80K substitution in the NS3 protease sequence at baseline. However, 24/28 such patients in cohort 1, and 10/11 in cohort 2 achieved an SVR [28]. More data is needed to assess whether this substitution should be sought in patients infected with subtype 1a by population sequencing (direct sequence analysis) prior to initiating the combination of sofosbuvir plus simeprevir, and whether patients with this substitution should also receive ribavirin or be proposed another therapy. No substitutions in the HCV RNA-dependent RNA polymerase region targeted by sofosbuvir were observed in patients who relapsed. Although both sofosbuvir and simeprevir are individually well tolerated and no safety signal was reported in the COSMOS trial, cautious monitoring will be needed in the absence of large-scale safety data for this combination.

Genotype 1, Option 6

Recommendations

- Patients infected with HCV genotype 1 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients, including those who failed on a triple combination of pegylated IFN- α , ribavirin and either telaprevir or boceprevir (pending data with 12 weeks of therapy in treatment-experienced patients) (**Recommendation B1**)
- Preliminary results do not indicate a major advantage to adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B1**)

Comments: Phase IIb results have been recently published with this combination [29]. With 24 weeks of therapy, the SVR rates were 100% (14/14 and 15/15, with and without ribavirin, respectively) in treatment-naïve patients, and 100% (21/21) and 95% (19/21), 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) [29]. One patient who had experienced HCV recurrence after liver transplantation was cured with this combination [30]; other cases, while undoubtedly treated in expanded access programs, have not been fully reported. The impact of pre-existing substitutions in the NS5A protein sequence known to confer resistance to daclatasvir at baseline on the response is unknown. Given the high SVR rates, regardless of subtype, resistance testing is not recommended. Although both sofosbuvir and daclatasvir are individually well tolerated and no safety signal was reported in the Phase II trials, cautious monitoring will be needed in the absence of large-scale safety data for this combination.

4.7.2. Treatment of HCV genotype 2 infection

The best treatment option for patients infected with HCV genotype 2 is the combination of sofosbuvir and ribavirin. In settings where this option is not available, the combination of pegylated IFN- α and ribavirin remains acceptable [2].

Genotype 2, Option 1

Recommendations

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

Comments: Results from 4 Phase III trials have been published. In the FISSION trial in treatment-naïve patients treated 12 weeks [18], the SVR rate was 95% (69/73). The response rate was better in patients without cirrhosis (97% vs. 83% in patients without and with cirrhosis, respectively). The POSITRON trial included patients considered ineligible or intolerant to IFN, who were treated 12 weeks with sofosbuvir and ribavirin [31]. SVR was achieved in 93% (101/109) of cases. When comparing 12 and 16 weeks of therapy in the FUSION trial [31], SVR was achieved in 82% (32/39) and 89% (31/35) of cases, respectively, 60% (6/10) and 78% (7/9) in patients with cirrhosis, respectively. This indicates that patients with cirrhosis may benefit from longer than 12 weeks of therapy. In the VALENCE trial [32], the SVR rates after 12 weeks of treatment were 97% (29/30) in treatment-naïve non-cirrhotic individuals, 100% (2/2) in treatment-naïve cirrhotics, 91% (30/33) in treatment-experienced non-cirrhotics, and 88% (7/8) in treatment-experienced cirrhotics. The combination of sofosbuvir and ribavirin was well tolerated. No virological breakthroughs were observed in treatment-adherent patients, and relapses were not associated with the selection of resistant HCV variants.

Genotype 2, Option 2

Recommendation

- Alternatively, cirrhotic and/or treatment-experienced patients could be treated with weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation B1**)

Comments: In the LONESTAR-2 Phase IIb study [33], a single centre study in which 23 treatment-experienced patients infected with HCV genotype 2, including 14 with cirrhosis, received 12 weeks of pegylated IFN- α , ribavirin, and sofosbuvir, the SVR rate was 96%.

4.7.3. Treatment of HCV genotype 3 infection

Three treatment options are available for patients infected with HCV genotype 3. Based on data with other genotypes and preliminary results in a small group of genotype 3-infected patients, the triple combination of pegylated IFN- α , ribavirin, and sofosbuvir (Option 1) appears to be more efficacious with a shorter duration than the combination of sofosbuvir and ribavirin (Option 2), which is suboptimal in patients with cirrhosis and who have previously failed IFN and ribavirin. Although few data are available, the combination of sofosbuvir and daclatasvir, with or without ribavirin, is an attractive IFN-free option for patients infected with HCV genotype 3. In settings where none of these options is available, the combination of pegylated IFN- α and ribavirin remains acceptable [2].

Genotype 3, Option 1

Recommendation

- Patients infected with HCV genotype 3 can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation A2**)

Comments: This combination has been evaluated in 10 treatment-naïve non-cirrhotic patients infected with genotype 3. Nine of them achieved an SVR whereas the remaining one was lost to follow-up [34]. In addition, data with this combination in patients infected with HCV genotype 3 are available from the LONESTAR-2 Phase IIb trial in treatment-experienced individuals [33], who achieved an SVR in 83% (20/24) of cases, including 10/12 patients with cirrhosis. However, the pangenotypic activity of sofosbuvir, together with high SVR rates with other genotypes (89% (259/291) overall for genotypes 1 and 4 to 6), indicate that this combination can be safely used in patients infected with HCV genotype 3.

Genotype 3, Option 2

Recommendations

- Patients infected with HCV genotype 3 can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation A2**)
- This therapy is suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option (**Recommendation A2**)

Comments: Results from 4 Phase III trials have been published. In the FISSION trial in treatment-naïve patients treated 12 weeks [18], the SVR rate was 56% (102/183). The response rate was better in patients without cirrhosis (61% vs. 34% in patients without and with cirrhosis, respectively). The POSITRON trial included patients ineligible or intolerant to IFN-based therapy who were treated for 12 weeks with sofosbuvir and ribavirin [31] SVR was achieved in 61% (60/98) of cases. When comparing 12 and 16 weeks of therapy in the FUSION trial [31], SVR was achieved in 30% (19/64) and 62% (39/63) of cases, respectively, 19% (5/26) and 61% (14/23) in patients with cirrhosis, respectively. In the VALENCE trial [32], the SVR rates after 24 weeks of treatment were 94% (86/92) in treatment-naïve non-

cirrhotic individuals, 92% (12/13) in treatment-naïve cirrhotics, 87% (87/100) in treatment-experienced non-cirrhotics, and 60% (27/45) in treatment-experienced cirrhotics. The combination of sofosbuvir and ribavirin was well tolerated and very few patients stopped therapy. Haemoglobin declines are not generally problematic therefore. These results indicate that 24 weeks is the appropriate duration for this regimen in patients infected with HCV genotype 3, and that this regimen is suboptimal in treatment-experienced patients with cirrhosis. No virological breakthroughs were observed in treatment-adherent patients, and relapses were not associated with the selection of resistant HCV variants.

Genotype 3, Option 3

Recommendations

- Patients infected with HCV genotype 3 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients) (**Recommendation B1**)
- Preliminary results do not indicate a major impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B1**)

Comments: Little data is available with this combination in patients infected with genotype 3. However, daclatasvir has been shown to be active against this genotype both *in vitro* and *in vivo*. In a Phase IIb trial with this combination 24 weeks [29], the SVR rate was 89% (16/18) in treatment-naïve non-cirrhotic patients infected with HCV genotype 3. Ribavirin did not appear to have an impact on the SVR in this small series of patients. The response rates in previously treated genotype 3 patients with cirrhosis is not yet known and the optimal duration and need for ribavirin for 12 weeks treatment is unclear.

The impact of pre-existing substitutions in the NS5A protein sequence known to confer resistance to daclatasvir at baseline on the response is unknown. Given the high SVR rates, testing is not recommended. Although both sofosbuvir and daclatasvir are individually well tolerated and no safety signal was reported in the Phase II trials, cautious monitoring will be needed in the absence of large-scale safety data for this combination.

4.7.4. Treatment of HCV genotype 4 infection

Six treatment options are available for patients infected with HCV genotype 4, including IFN/ribavirin-containing and IFN-free ones. Regardless of the respective costs of these options, the triple combination of pegylated IFN-α, ribavirin, and sofosbuvir (Option 1) appears as the most efficacious and the easiest to use IFN-containing option, without the risk of selecting resistant viruses in case of treatment failure. The combination of sofosbuvir and simeprevir with or without ribavirin (Option 5) and the combination of sofosbuvir and daclatasvir with or without ribavirin (Option 6) appear as attractive, but data with these combinations is lacking in patients infected with HCV genotype 4. In settings where none of these options is available, the combination of pegylated IFN-α and ribavirin remains acceptable [2].

Genotype 4, Option 1

Recommendation

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

Comments: This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients [18]. The SVR rate in genotype 4 patients was 96% (27/28). The patient who failed on this regimen did not select HCV variants resistant to sofosbuvir. No data with this regimen has been presented in treatment-experienced patients or in HIV-coinfected patients. Whether longer treatment duration would be needed in the most difficult-to-treat population is unknown.

Genotype 4, Option 2

Recommendations

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

Comments: Simeprevir has been shown to be active against genotype 4 *in vitro*. Preliminary Phase III data which form part of the submission to the EMA in 107 patients infected with genotype 4 indicate that the combination of pegylated IFN-α, ribavirin, and simeprevir is effective (Moreno *et al.*, unpublished). Indeed, SVR was achieved in 89% (31/35) of treatment-naïve patients, 86% (19/22) of prior relapsers, 100% (10/10) of prior partial responders, and 75% (30/40) of prior null responders. No patient had a Q80K substitution detectable in the NS3 protease sequence at baseline.

Genotype 4, Option 3

Recommendations

- Patients infected with HCV genotype 4 can be treated with a combination of weekly pegylated IFN- α , daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily daclatasvir (60 mg) 24 weeks (**Recommendation B1**)
- Daclatasvir should be administered 12 weeks in combination with pegylated IFN- α and ribavirin. Daclatasvir should be continued in combination with pegylated IFN- α and ribavirin an additional 12 weeks (total duration 24 weeks) in patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10. Pegylated IFN- α and ribavirin should be continued alone between week 12 and 24 (total duration 24 weeks) in patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 (**Recommendation B1**)

Comments: Although this combination is theoretically effective, few data is available. The SVR rate was 100% (12/12) in the COMMAND-1 trial [23].

Genotype 4, Option 4

Recommendation

- Patients infected with HCV genotype 4 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation C2**)

Comments: Only preliminary data is available (SVR at week 4 post-treatment) in a small number of American patients of Egyptian ancestry [35]. The preliminary SVR rates were 79% (11/14) and 100% (14/14) after 12 and 24 weeks of treatment, respectively, in treatment-naïve patients, and 59% (10/17) and 93% (14/15) after 12 and 24 weeks, respectively, in treatment-experienced patients.

Genotype 4, Option 5

Recommendations

- Patients infected with HCV genotype 4 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily simeprevir (150 mg) 12 weeks (**Recommendation B2**)
- There is no data on the impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B2**)

Comments: There is no data with this combination in patients infected with HCV genotype 4. Nevertheless, given the antiviral effectiveness of both sofosbuvir and simeprevir against this genotype, it is likely that the results of the COSMOS trial in patients infected with genotype 1 can be extrapolated [28].

Genotype 4, Option 6

Recommendations

- Patients infected with HCV genotype 4 can be treated with an interferon-free combination of daily sofosbuvir (400 mg) and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients (pending data with 12 weeks of therapy in treatment-experienced patients) (**Recommendation B2**)
- There is no data on the impact of adding ribavirin to this regimen. However, adding daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively) should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis (**Recommendation B2**)

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

4.7.5. Treatment of HCV genotype 5 or 6 infection

The only treatment option for patients infected with HCV genotypes 5 or 6 is the triple combination of pegylated IFN- α , ribavirin and sofosbuvir. Patients who are intolerant or ineligible to IFN-based therapy should receive the combination of sofosbuvir and ribavirin. In settings where none of these options is available, the combination of pegylated IFN- α and ribavirin remains acceptable [2].

Genotype 5 or 6, Option 1

Recommendation

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

Comments: This combination has been evaluated in the NEUTRINO Phase III trial in treatment-naïve patients [18]. The single patient with genotype 5 and all 6 patients with genotype 6 achieved an SVR. No data with this regimen has been presented in treatment-experienced or HIV-coinfected patients. Whether longer treatment duration would be needed in the most difficult-to-treat population is unknown.

Genotype 5 or 6, Option 2

Recommendation

- Patients infected with HCV genotype 5 or 6 who are IFN-intolerant or -ineligible can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively), and daily sofosbuvir (400 mg) 24 weeks (**Recommendation C2**)

Comments: No data is available with this combination for these rare genotypes.

4.8. Treatment monitoring

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

4.8.1. 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 [36-38]. In order to monitor treatment efficacy and eventually guide decisions on treatment duration, HCV RNA level measurements should be performed at specific time points. Measurements should only be made if and when the result of the measurement will have some influence on the scheduled treatment, i.e., to assess patient adherence to therapy (week 2 determination), if the result will determine that treatment should be abandoned (futility rules), that treatment can be abbreviated (response-guided therapy), or that treatment has been successful (end of treatment and post-treatment SVR assessment). Little is known about the impact of the analytical sensitivity and lower limits of detection or quantification of different HCV RNA assays for assessment of futility rules and determination of treatment duration.

Recommendations

Recommendations

- A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy (**Recommendation A1**)
- In patients treated with the triple combination of pegylated IFN- α , ribavirin and sofosbuvir 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)
- In patients treated with the triple combination of pegylated IFN- α , ribavirin and simeprevir (12 weeks plus 12 or 36 weeks of pegylated IFN- α and ribavirin alone), HCV RNA should be measured at baseline, week 4, week 12, week 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)
- In patients treated with the triple combination of pegylated IFN- α , ribavirin and daclatasvir 24 weeks (12 weeks plus 12 weeks of pegylated IFN- α and ribavirin alone, or 24 weeks of the triple combination), HCV RNA should be measured at baseline, week 4, week 10, week 24 (end of treatment), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)
- In patients treated with an IFN-free regimen (sofosbuvir plus simeprevir with or without ribavirin 12 weeks, sofosbuvir plus daclatasvir with or without ribavirin 12 or 24 weeks, sofosbuvir plus ribavirin 12 or 24 weeks), HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy (**Recommendation A2**)

4.8.2. Stopping (futility) rules

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

Recommendations

Recommendations

- With the triple combination of pegylated IFN- α , ribavirin and simeprevir, treatment should be stopped if HCV RNA level is ≥ 25 IU/ml at treatment week 4, week 12 or week 24 (**Recommendation A2**)
- No futility rules have been defined for other treatment regimens (**Recommendation A1**)

4.8.3. Virological response-guided triple therapy

Response-guided therapy is used only for the triple combination of pegylated IFN- α , ribavirin, and daclatasvir.

Recommendations

Recommendations

- With the triple combination of pegylated IFN- α , ribavirin and daclatasvir, patients who do not achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 should receive the 3 drugs 24 weeks. Patients who achieve an HCV RNA level <25 IU/ml at week 4 and undetectable at week 10 should stop daclatasvir at week 12 and continue with pegylated IFN- α and ribavirin alone until week 24 (**Recommendation A2**)
- No response-guided therapy is used in other treatment regimens (**Recommendation A1**)

4.8.4. Monitoring treatment safety

Flu-like symptoms are often present after pegylated IFN- α injections. They are easily controlled by paracetamol and tend to attenuate after 4-6 weeks of therapy. At each visit, the patients should be assessed for clinical side effects, such as severe fatigue, depression, irritability, sleeping disorders, skin reactions and dyspnoea. Thyroxine and thyroid stimulating hormone (TSH) levels should be measured every 12 weeks while on therapy [39].

Haematological side effects of pegylated IFN- α and ribavirin include neutropenia, anaemia, thrombocytopenia, and lymphopenia. These parameters should be assessed at weeks 1, 2, and 4 of therapy and at 4 to 8 week intervals thereafter. Mild anaemia can occur in regimens containing ribavirin; haemoglobin decreases have been greater and more common when DAAs were combined with ribavirin than in regimens without ribavirin.

Sofosbuvir, simeprevir, and daclatasvir are generally well tolerated. Headache and fatigue have been reported with sofosbuvir. The renal function should be checked regularly in patients receiving sofosbuvir. Patients receiving simeprevir may experience mild to moderate rashes and photosensitivity; indirect hyperbilirubinaemia may occur, but the concentration rises in patients not receiving ribavirin are lower. Thus far, no side effects required withdrawal of any of these DAAs. Frequencies of high grade or serious adverse events leading to discontinuation of IFN-free regimens are low. The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment. In patients receiving calcineurin inhibitors, therapeutic drug monitoring should be performed regularly during treatment and within 2 weeks following simeprevir or daclatasvir withdrawal.

Recommendations

Recommendations

- The patients receiving pegylated IFN- α and ribavirin should be assessed for clinical side effects at each visit, while the haematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter (**Recommendation A1**)
- Renal function should be checked regularly in patients receiving sofosbuvir (**Recommendation B1**)
- Rashes and bilirubin elevations may be seen with simeprevir (**Recommendation A1**)
- The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment (**Recommendation A1**)

4.8.5. Treatment dose reductions

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

If significant anaemia occurs (haemoglobin $<10 \text{ g/dl}$), the dose of ribavirin should be adjusted downward by 200 mg at decrements. A more rapid reduction of dose may be required for patients with rapidly declining haemoglobin, particularly if the baseline haemoglobin was low. Ribavirin administration should be stopped if the haemoglobin level falls below 8.5 g/dl [39-47].

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

No dose adjustments are recommended for sofosbuvir, simeprevir or daclatasvir.

4.9. Measures to improve treatment adherence

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

Before starting antiviral therapy, patients must be instructed about the schedule and the eventual side effects (IFN and ribavirin containing regimens) to be expected during treatment. Patients should also be instructed about the preventive and therapeutic measures to ameliorate these side effects, for example by using antipyretics, analgesics, or antidepressants if they receive IFN. Regular follow-up visits must be scheduled so that treatment progress and management of eventual 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, drug and alcohol services, psychiatric services, 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 [48, 49]. 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 is becoming easier with the new therapeutic regimens.

Alcohol consumption has an impact on treatment adherence [50]. 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 [50-53]. Pharmacists should advise on potential drug-drug interactions.

Recommendations

Recommendations

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

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

Non-cirrhotic patients who achieve an SVR should be retested for HCV RNA at 48 weeks post-treatment. If HCV RNA is still not detected, the infection can be considered as definitely eradicated and HCV RNA need not be retested. As hypothyroidism may occur after stopping IFN therapy, thyroxin and TSH levels should also be assessed 1 and 2 years after treatment if the patient has received IFN. Patients with pre-existing cofactors of liver disease (notably, history of alcohol drinking and/or type 2 diabetes) should be carefully and periodically

subjected to a thorough clinical assessment, as needed.

Cirrhotic patients who achieve an SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy (though first variceal bleed is seldom observed after SVR). The presence of cofactors of liver disease, such as history of alcohol drinking and/or type 2 diabetes may determine that additional assessments are necessary.

There remains some concern that re-infection due to recurrent or persistent risk behaviour may negate the potential benefit of treatment. Reported rates of re-infection following successful HCV treatment among patients at high risk, such as people who inject drugs (PWID), or men who have sex with men (MSM) are low, with estimates of 1-5% risk per year [54-58].

Recommendations

Recommendations

- Non-cirrhotic patients with SVR should be retested for ALT and HCV RNA at 48 weeks post-treatment, then discharged if ALT is normal and HCV RNA is negative (**Recommendation C2**)
- Cirrhotic patients with SVR should undergo surveillance for HCC every 6 months by means of ultrasound (**Recommendation B1**)
- Guidelines for management of portal hypertension and varices should be implemented, though index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for on-going liver damage are present and persist) (**Recommendation A2**)
- Patients with on-going drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection (**Recommendation B1**)
- Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on PWID or MSM with on-going risk behaviour (**Recommendation B2**)

4.11. Retreatment of non-sustained virological responders

In patients infected with genotype 1 who did not respond to the combination of pegylated IFN- α , ribavirin, and either telaprevir or boceprevir, 24 weeks of the combination of sofosbuvir and daclatasvir yielded SVR rates of 100% (21/21) and 95% (19/21) with and without ribavirin, respectively [29]. No data with sofosbuvir, pegylated IFN- α and ribavirin has been presented in this population.

There is currently no retreatment data available in patients who failed to achieve an SVR with the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir. Sofosbuvir has not been reported to select clinically meaningful resistant HCV variants in case of treatment failure. In contrast, patients exposed to simeprevir or daclatasvir who fail on treatment will harbour viruses with amino acid substitutions conferring drug resistance in the NS3 protease and NS5A regions, respectively. Viruses resistant to protease inhibitors generally progressively decrease in proportion to become undetectable by means of population sequencing (direct sequence analysis) within a few months to 2 years. In contrast, viruses resistant to NS5A inhibitors are very fit and remain for many years, perhaps forever, after they have been selected by a treatment including an NS5A inhibitor [59-62].

Whether assessing the sequence of the target HCV proteins (HCV resistance testing) prior to retreatment is helpful to make a decision remains unknown, as well as which therapeutic decision should be made based on this result.

Intuitively, patients who failed on a regimen containing sofosbuvir as the only DAA could be retreated with a combination of sofosbuvir and simeprevir, or a combination of simeprevir and daclatasvir; patients who failed on a regimen containing simeprevir as the only DAA could be retreated with a combination of sofosbuvir and daclatasvir; finally, patients who failed on a regimen containing daclatasvir as the only DAA could be retreated with a combination of sofosbuvir and simeprevir. Patients who failed on a regimen containing sofosbuvir and simeprevir could be retreated with a combination of sofosbuvir and daclatasvir, whereas patients who failed on a regimen containing sofosbuvir and daclatasvir could be retreated with a combination of sofosbuvir and simeprevir. None of these options has been fully validated in a clinical trial. Another option, when possible, is to wait until alternative therapeutic options become available.

Recommendations

Recommendations

- Patients who failed on a regimen containing sofosbuvir as the only DAA can be retreated with a combination of sofosbuvir and simeprevir (genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes) (**Recommendation B1**)
- Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only DAA can be retreated with a combination of sofosbuvir and daclatasvir (**Recommendation B1**)
- Patients who failed on a regimen containing daclatasvir as the only DAA can be retreated with a combination of sofosbuvir and simeprevir (genotypes 1 or 4 only) (**Recommendation B1**)
- Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir (**Recommendation B1**)
- Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (genotypes 1 or 4 only) (**Recommendation B1**)
- Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy (**Recommendation B1**)
- The utility of HCV resistance testing (i.e. the determination of the sequence of the DAA target region) prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown (**Recommendation B2**)

4.12. Treatment of patients with severe liver disease

4.12.1. Compensated cirrhosis

Treatment is strongly recommended for patients with compensated cirrhosis, in order to prevent the complications of chronic HCV infection that occur in this group in the short to mid-term. Indeed, large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significant decrease of the incidence of clinical decompensation and HCC [63, 64]. However, the SVR rates are generally lower, even with the new therapies, in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis. Particular care should be taken in monitoring

and management of the side effects in this group of patients, who are generally older, have other comorbidities, may be receiving other medication and have a worse tolerance than patients with less advanced liver disease.

If a 12-24 week IFN-based regimen is considered tolerable in patients with compensated cirrhosis and good liver function, these patients can be treated as recommended above across genotypes. However as data emerges, IFN-free treatment strategies could be considered preferable in patients with cirrhosis who have not had an episode of decompensation. Thus, deferring these patients may be considered. IFN is contraindicated in patients with decompensated cirrhosis. These patients at high risk should be offered what is considered an optimal genotype-centred IFN-free regimen, eventually via expanded access programs if available. Irrespective of deferral or the achievement of an SVR, patients with cirrhosis should undergo regular surveillance for the occurrence of HCC and for portal hypertension, as the risk of complications is decreased but not abolished when HCV infection has been eradicated.

Recommendations

Recommendations

- Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications (**Recommendation A1**)
- IFN-free combination regimens should be preferred in patients with compensated cirrhosis (**Recommendation B1**)
- If a 12-24 week IFN-based DAA regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopaenia, these patients can be treated as recommended above across genotypes (**Recommendation B1**)
- Patients with cirrhosis should undergo regular surveillance for HCC, irrespective of SVR (**Recommendation A1**)

4.12.2. Patients with an indication for liver transplantation

Liver transplantation (LT) is the treatment of choice for patients with end-stage liver disease. However, hepatitis C recurrence due to graft infection is universal after transplantation in the absence of prevention [65], and the life of the graft is reduced in patients with recurrent hepatitis C. An initial report of the use of pre-transplant sofosbuvir and ribavirin for up to 48 weeks stopping on day of transplant has been presented. Forty-four patients infected with HCV genotypes 1 to 4 with hepatocellular carcinoma were treated with the combination of sofosbuvir and ribavirin [66]; 41 of them (93%) were HCV RNA undetectable on treatment at the time of transplantation. Among them, 64% were HCV RNA undetectable off therapy 12 weeks after transplantation (25/39 patients who reached week 12 post-transplant), i.e., achieved an SVR with no recurrence of HCV infection on the graft. The duration of undetectable HCV RNA pre-transplant was the best predictor of response (undetectable HCV RNA for more than 30 continuous days). Although no data has been generated with other drug combinations, it is likely that adding a second DAA, with or

without ribavirin, will yield more efficient prevention of HCV recurrence post-transplant. Patients with low MELD scores and HCC could be also be considered for a 12-week IFN-containing DAA regimen prior to transplantation.

Whether patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) should be treated with the same regimens remains unknown, in the absence of published or reported data. Direct-acting antiviral drugs are equally effective against their viruses; however, patients with advanced liver disease generally need more time and/or more potent antiviral intervention to eliminate HCV. Little is known about the safety of several HCV drug combinations in patients with decompensated disease. The pharmacokinetics of sofosbuvir and daclatasvir do not appear to change significantly in patients with moderate or severe liver impairment [67]. Finite treatment strategies could stabilise a proportion of patients, leading to their delisting or their proceeding to transplant with undetectable HCV RNA and low rates of post-transplant recurrence. Other patients may require treatment to the day of transplant.

Thus, antiviral therapy is indicated in patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC. In patients with Child-Pugh B or C cirrhosis awaiting transplantation, antiviral therapy may be offered on an individual basis in experienced centres, pending the presentation of more data in this population. The effect of viral clearance on liver function and portal hypertension in this group of patients remains unknown.

It is possible that patients with decompensated cirrhosis who are not on a transplant list could benefit from an IFN-free treatment regimen. However the safety and efficacy of an IFN-free regimen in patients with decompensated cirrhosis not on a transplant waiting list is unknown, and the impact on mortality in this group is not yet established.

Recommendations

Recommendations

- In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation (**Recommendation A1**)
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC should be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) until liver transplantation (**Recommendation A1**)
- Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC can also be treated with a combination of weekly pegylated IFN-α, daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) 12 weeks (**Recommendation B1**)
- In patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is HCC, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant. Therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), daily sofosbuvir (400 mg), and daily daclatasvir (60 mg) 12 weeks prior to transplantation (**Recommendation B1**)

Recommendations (continued)

- Patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) can be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg) until liver transplantation in experienced centres under close monitoring. IFN is contraindicated in these patients (**Recommendation B1**)
- The addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant. Therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh B and C) with genotype 1 to 4 infection should be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), daily sofosbuvir (400 mg), and daily daclatasvir (60 mg) until liver transplantation in experienced centres under close monitoring (**Recommendation B1**)
- Patients with decompensated cirrhosis not on a transplant waiting list should only be offered an IFN-free regimen within a clinical trial, an expanded access program or within experienced centres, because the efficacy, safety and outcomes have not yet been established for this group (**Recommendation B1**)

4.12.3. Post-liver transplantation recurrence

HCV infection recurrence is universal in patients with detectable HCV RNA at the time of liver transplantation [65]. 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 [68, 69]. Successful therapy has been shown to have a positive impact on both graft and patient survival [70].

Patients with post-transplant recurrence of HCV infection should be considered for therapy. These patients generally have a better background for therapy than at the acute stage of graft infection, i.e., less immunosuppression. The presence of significant fibrosis or portal hypertension one year after transplantation is predictive of rapid disease progression and graft loss, and urgently indicates antiviral treatment [71, 72].

Published efficacy data are limited. The combination of sofosbuvir and ribavirin yielded an SVR rate 4 weeks after the end of therapy of 77% in 40 patients with post-transplant HCV recurrence (on-going study). One liver transplant recipient with severe recurrent cholestatic hepatitis C was reported to be cured by the combination of sofosbuvir and daclatasvir [30]. Similar cases were reported with the combination of sofosbuvir and ribavirin or sofosbuvir and daclatasvir in the framework of early access programs.

Drug-drug interactions may be important in the post-transplant setting. No clinically significant drug-drug interactions have been found between sofosbuvir, simeprevir or daclatasvir on the one hand, and cyclosporine and tacrolimus on the other hand.

Recommendations

Recommendations

- Patients with post-transplant recurrence of HCV infection should be considered for therapy. Significant fibrosis or portal hypertension one year after transplantation predict rapid disease progression and graft loss, and indicate more urgent antiviral treatment (**Recommendation B2**)
- Patients with HCV genotype 2 infection must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg), 12 to 24 weeks, pending more data in this population (**Recommendation B1**)
- Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with daily sofosbuvir (400 mg), and daily daclatasvir (60 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), pending more data in this population (**Recommendation B1**)
- Patients with HCV genotype 1 or 4 infection can be treated with daily sofosbuvir (400 mg), and daily simeprevir (150 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), pending more data in this population (**Recommendation B1**)
- No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is however important in the absence of safety data in this population (**Recommendation B1**)

4.13. Treatment of special groups

4.13.1. HBV co-infection

In patients with HCV-HBV co-infection, 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 mono-infected patients. There is a potential risk of HBV reactivation during or after HCV clearance [73]. In that case, or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. Simeprevir increases exposure to tenofovir. Thus, in patients receiving tenofovir as anti-HBV treatment, the estimated glomerular filtration rate and tubular function should be monitored frequently during treatment and tenofovir doses should be consequently adjusted.

Recommendations

Recommendations

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

4.13.2. Treatment of patients with co-morbidities

Haemodialysis patients. HCV infection is prevalent in the haemodialysis population and is associated with an increased risk for all-cause and liver-related mortality. Cardiovascular disease remains, however, the main cause of death in dialysis patients irrespective of HCV status. As in all settings, the candidacy of a dialysis patient for antiviral therapy requires special consideration of co-morbid conditions, since the liver disease may have little impact on predicted morbidity and mortality of that patient. HCV-associated liver damage may be accelerated by immunosuppression. For this reason, antiviral therapy should be considered for all haemodialysis patients who will be candidates for renal transplantation. The use of ribavirin is problematic in this setting. Individualized ribavirin dosing of 200 mg/day or 200 mg/every other day or 200 mg thrice weekly after haemodialysis is recommended, and substantial hematopoietic support is essential. There are no published data to describe the pharmacokinetics, dosing safety and efficacy of current IFN-free anti-HCV regimens in haemodialysis patients. This is an urgent unmet need.

Recommendations

Recommendations

- Haemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy (**Recommendation B1**)
- Haemodialysis patients should receive an IFN-free, if possible ribavirin-free regimen. However, no safety dosing and efficacy data is available in this population, and the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate (eGFR) $<30\text{ml/min/1.73m}^2$ or with end-stage renal disease until more data is available (**Recommendation 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 studies of kidney transplant cohorts show that HCV positivity is associated with impaired renal graft and patient survival. Impaired graft survival partly reflects increased patient mortality. In addition, specific HCV-related causes such as glomerulonephritis and increased risk of diabetes will affect graft outcome. HCV positivity is associated with increased all-cause and liver-related mortality, though cardiovascular disease remains the main cause of patient death [74]. 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 [75]. For patients with established cirrhosis and portal hypertension who fail (or are unsuitable for) HCV antiviral treatment, isolated renal transplantation may be contraindicated and consideration should be given to combined liver and kidney transplantation [76]. As IFN-based treatment may lead to graft rejection, there is an urgent need to offer these patients IFN-free regimens.

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

International guidelines list chronic HCV infection as a contraindication to lung transplantation [77]. Treatment of lung

transplant candidates before transplantation has been recommended by some authors, but there is limited experience with this approach. No data are available on the impact of HCV infection and its treatment after pancreas or small bowel transplantation.

Recommendations

Recommendations

- HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. Where possible, antiviral therapy should be given to potential transplant recipients before listing for renal transplantation. These patients should receive an IFN-free, if possible ribavirin-free regimen. However, no safety and efficacy data is available in this population, and the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate (eGFR) $<30\text{ml/min/1.73m}^2$ or with end-stage renal disease until more data is available (**Recommendation A2**)
- In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an IFN-free regimen (**Recommendation A2**)
- Patients with HCV genotype 2 infection must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients $<75\text{ kg}$ or $\geq 75\text{ kg}$, respectively), and daily sofosbuvir (400 mg), 12 to 24 weeks, pending more data in this population (**Recommendation B1**)
- Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with daily sofosbuvir (400 mg), and daily daclatasvir (60 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients $<75\text{ kg}$ or $\geq 75\text{ kg}$, respectively), pending more safety data in this population (**Recommendation B1**)
- Patients with HCV genotype 1 or 4 infection can be treated with daily sofosbuvir (400 mg), and daily simeprevir (150 mg), 12 to 24 weeks, with or without daily weight-based ribavirin (1000 or 1200 mg in patients $<75\text{ kg}$ or $\geq 75\text{ kg}$, respectively), pending more data in this population (**Recommendation B1**)
- No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is however important in the absence of safety data in this population (**Recommendation B1**)

Active drug addicts and patients on stable maintenance substitution. Ageing cohorts of PWIDs with chronic HCV and low treatment uptake are making a significant contribution to the population with advanced liver disease and to liver-related mortality [78, 79]. The prevalence of HCV among PWIDs is ~65% [80-82] and >80% among long-term PWIDs [80].

HCV treatment must be considered for PWIDs, provided they wish to receive treatment and are able and willing to maintain regular appointments. Guidelines for pre-therapeutic assessment for HCV-infected individuals are available [2, 83]. Modelling studies suggest that implementation of HCV treatment for PWIDs could reduce transmission [84, 85]. Decisions to treat must be made on a case-by-case basis. PWIDs with on-going social issues and/or with a history of psychiatric disease or with more frequent drug-use during therapy are at risk of lower adherence and reduced likelihood of achieving

SVR and need to be monitored closely during therapy, and also need more supporting measures.

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

DAA clinical development programs have excluded individuals with active drug use, but many trials have included those on opioid substitution therapy. DAA-based safety and treatment outcome data has not been presented on clinical trial sub-populations of individuals on opioid substitution therapy. Drug-drug interaction studies have been undertaken with sofosbuvir and simeprevir on the one hand, methadone [86] and buprenorphine [87] on the other hand, with no clinically important interactions observed. Interaction studies with daclatasvir and methadone/buprenorphine are underway.

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

Recommendations

Recommendations

- PWIDs should be routinely and voluntarily tested for HCV antibodies and if negative, every 6-12 months (**Recommendation B1**)
- PWIDs should be provided with clean drug injecting equipment and access to opioid substitution therapy as part of widespread comprehensive harm reduction programs, including in prisons (**Recommendation B1**)
- Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk and harm reduction strategies (**Recommendation B1**)
- PWIDs should be counselled to moderate alcohol intake, or to abstain if there is evidence of advanced liver disease (**Recommendation A1**)
- PWIDs should be counselled to moderate cannabis use, or to abstain if there is evidence of advanced liver disease (**Recommendation B2**)
- HCV treatment for PWIDs should be considered on an individualized basis and delivered within a multidisciplinary team setting (**Recommendation A1**)
- Pre-therapeutic assessment should include an evaluation of housing, education, cultural issues, social functioning and support, finances, nutrition and drug and alcohol use. PWID should be linked into social support services and peer support, if available (**Recommendation A1**)
- A history of IDU 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 (**Recommendation B1**)

Recommendations (continued)

- 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 (**Recommendation B1**)
- Evaluation of safety and efficacy of new IFN-containing and IFN-free regimens in PWIDs is needed (**Recommendation C1**)
- Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir (**Recommendation B2**)
- Consideration of IFN-containing or IFN-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies (**Recommendation B2**)
- The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs (**Recommendation B1**)
- Awareness should be raised that liver transplantation is a therapeutic option in those with a history of IDU (**Recommendation 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 (**Recommendation 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. No trials with antiviral therapy have been published in this population. Treatment has often been withheld in these patients because both pegylated IFN- α and ribavirin can cause anaemia. In the absence of published studies to examine the safety of treatment regimens based on sofosbuvir, simeprevir and/or daclatasvir in patients with haemoglobinopathies, there is no reason to consider that these drugs are specifically contraindicated. Thus, IFN-free, ribavirin-free drug regimens should be used in these patients because they have the great advantage of not aggravating the anaemia.

Recommendations

Recommendations

- The indications for HCV therapy are the same in patients with and without haemoglobinopathies (**Recommendation A1**)
- Given that both drugs cause anaemia, the use of pegylated IFN- α and ribavirin should be avoided in patients with haemoglobinopathies, when possible. When the use of ribavirin is needed, careful monitoring is recommended, and blood transfusions may be required (**Recommendation A2**)

Recommendations (continued)

- Patients with haemoglobinopathies with HCV genotype 2 infection must be treated with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily sofosbuvir (400 mg), 12 to 24 weeks (pending more data in this population) **(Recommendation B2)**
- Patients with haemoglobinopathies with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with an interferon-free combination of daily sofosbuvir (400 mg), and daily daclatasvir (60 mg) 12 weeks in treatment-naïve patients or 24 weeks in treatment-experienced patients **(Recommendation B2)**
- Patients with haemoglobinopathies with HCV genotype 1 or 4 infection can be treated with an interferon-free combination of daily sofosbuvir (400 mg), and daily simeprevir (150 mg) 12 weeks **(Recommendation B2)**

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

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

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 hours, after which no further concentrate is required. Co-infection with HIV/HCV is not a contraindication to liver transplantation in haemophilia. The indications for liver transplantation in humans with haemophilia are the same as non-haemophilic individuals, but the procedure has the major advantage of producing a phenotypic cure of the haemophilia as a result of factor VIII production by the transplanted liver.

Recommendations

Recommendations

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

4.14. 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. For patients who have failed prior treatment with pegylated IFN- α and ribavirin or telaprevir/boceprevir-based triple therapy, the pattern of virological response and failure should be carefully documented. Untreated patients should be assessed every 1 to 2 years with a non-invasive method. Patients with cirrhosis should undergo specific surveillance for HCC every 6 months.

Recommendations

Recommendations

- Untreated patients with chronic hepatitis C and those who failed prior treatment should be regularly followed **(Recommendation A1)**
- Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals **(Recommendation A2)**
- HCC surveillance must be continued indefinitely in patients with cirrhosis **(Recommendation A1)**

4.15. 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, female gender, a young age, and genetic polymorphisms in the region upstream of the *IL28B* gene have been associated with spontaneous viral clearance, but none of these parameters accurately predicts spontaneous resolution at the individual level.

Patients with acute hepatitis C should be considered for antiviral therapy in order to prevent progression to chronic hepatitis C. High SVR rates (>90%) have been reported with pegylated IFN- α monotherapy, essentially in series of symptomatic patients, regardless of the HCV genotype. Combination therapy with ribavirin does not increase the SVR rate in this setting, but used to be considered during treatment in patients with slow response and other negative predictors of treatment response [88-93]. No data are available on the use of new treatment regimens based on sofosbuvir, simeprevir or daclatasvir in patients with acute hepatitis C.

The ideal time point for starting therapy has not been firmly established. Some investigators estimate that the onset of ALT elevation, with or without clinical symptoms, may be the ideal time point for treatment [94-97]. It has also been suggested that patients should be followed with 4-weekly HCV RNA quantification and that only those who remain HCV positive at 12 weeks from onset should be treated [98].

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

Recommendations

Recommendations

- Pegylated IFN- α monotherapy (pegylated IFN- α 2a, 180 μ g/week or pegylated IFN- α 2b, 1.5 μ g/kg/week) for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases (**Recommendation A1**)
- Pegylated IFN- α (pegylated IFN- α 2a, 180 μ g/week or pegylated IFN- α 2b, 1.5 μ g/kg/week) should be combined with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or $\geq$ 75 kg, respectively) for 24 weeks in patients with acute hepatitis C who are HIV-coinfected (**Recommendation B1**)
- Although no data is available yet, IFN-free regimens can theoretically be used in these patients and are expected to achieve high SVR rates. The same doses and durations as for patients with chronic hepatitis C must be used, until new data indicate whether shorter and/or less intensive treatment is sufficient to achieve high infection cure rates (**Recommendation B1**)

4.16. Perspective of new treatments

A large number of other HCV drugs have reached late clinical development. Phase III data have been presented for the combination of pegylated IFN- α , ribavirin and faldaprevir. Phase III data will be presented in April 2014 for the fixed-dose combination of sofosbuvir and ledipasvir, and for the three-drug combination of ritonavir-boosted ABT-450, ombitasvir (formerly ABT-267), and dasabuvir (formerly ABT-333). A large number of additional Phase II data has been and will be presented with other HCV drugs in development. Thus, these recommendations will be updated regularly, following approval of new drug regimens by the European Medicines Agency.

Conflict of interest

Jean-Michel Pawlotsky

Grant and research support: Gilead.

Advisory Boards: Abbott, Abbvie, Achillion, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Idenix, Janssen, Merck, Novartis, and Roche.

Speaking and teaching: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck, Novartis, and Roche.

Alessio Aghemo

Grant and research support: Roche and Gilead.

Advisory Boards: Abbvie, Gilead, and Janssen.

Speaking and teaching: Abbvie, Gilead, Janssen, Merck, and Roche.

Geoffrey Dusheiko

Grant and research support: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex.

Advisory Boards: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex.

Speaking and teaching: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, and Vertex.

Xavier Forns

Grant and research support: Janssen, Merck, and Roche.

Advisory Boards: Abbvie, Gilead, and Janssen.

Speaking and teaching: Abbvie, Gilead, and Janssen.

Massimo Puoti

Grant and research support: Gilead and Novartis.

Advisory Boards: Abbvie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck, Roche, and Vertex.

Speaking and teaching: Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Roche

Christoph Sarrazin

Grant and research support: Abbott, Abbvie, Gilead, Janssen, Qiagen, Roche, Siemens, and Vertex.

Advisory Boards: Abbott, Abbvie, Achillion, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, Janssen, Merck, Novartis, Roche, and Vertex.

Speaking and teaching: Abbot, Abbvie, Bristol-Myers Squibb, Boehringer-Ingelheim, Gilead, Janssen, Merck, Novartis, Qiagen, Roche, and Siemens.

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