AFEF guidelines
Management of hepatitis C virus infection

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(Société de Pathologie Infectieuse de Langue Française)
Chairs

Prof. Olivier Chazouillères (APHP Saint-Antoine)
Prof. Patrick Hillon (CHU Dijon)

Scientific Committee

Dr Hélène Fontaine (APHP Cochin),
Dr Bertrand Hanslik (Montpellier),
Prof. Christophe Hézode (APHP Créteil),
Prof. Víctor de Ledinghen (CHU Bordeaux),
Prof. Georges-Philippe Pageaux (CHU Montpellier),
Dr Christophe Renou (CH Hyères),
Prof. Dominique Salmon (APHP Cochin)
Prof. Albert Tran (CHU Nice),
Prof. Fabien Zoulim (CHU Lyon)

Contact and information : AFEF
General secretary
Pr Víctor de Ledinghen
victor.deledinghen@chu-bordeaux.fr
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APPENDICES
1. Introduction

The present recommendations issued by the AFEF (Association Française pour l’Etude du Foie) on the management of chronic hepatitis C virus infection aim to help carers, all individuals involved in patient management, and the patients themselves, in finding the best possible therapeutic approach with a view to controlling the hepatitis C virus epidemic in France. These AFEF recommendations originate from the Working Session which took place on 29 May 2015 in Paris (Appendix 1).

2. Management objectives

Hepatitis C virus infection is both a viral disease and a chronic liver disease. The main objective of treatment is to achieve sustained virologic response (SVR) which is undetectable HCV RNA 12 weeks after the end of treatment. SVR is generally associated with slow regression of hepatic lesions in non-cirrhotic patients (1). However, among cirrhotic patients, even if the risk of decompensated liver disease (liver failure, portal hypertension) disappears, the risk of hepatocellular carcinoma (HCC) does not completely disappear.

3. Methodology

The AFEF recommendations were drawn up by a panel of experts appointed by the board of the AFEF. These recommendations were approved by the board of the AFEF. The recommendations are based on written publications in peer-review journals, together with papers and posters presented during international conferences. The level of evidence of the recommendations is indicated according to the grading system adopted by the French National Authority for Health (Haute Autorité de Santé) adapted to the specific requirements of new drug development for hepatitis C.

A Established scientific evidence

Based on studies with a high level of evidence (level of evidence 1): randomised comparative trials with high power and without any major biases, or meta-analysis of randomised comparative trials, analysis of decisions based on properly conducted studies, phase 3 studies and multicentre cohort studies.
B Scientific assumption
Based on scientific assumption arising from studies with an intermediate level of evidence (level of evidence 2), such as randomised comparative trials with low power, properly conducted non-randomised comparative studies, phase 2 studies and single-centre cohort studies.

C Low level of evidence
Based on studies with a lower level of evidence, such as case-control studies (level of evidence 3), retrospective studies, case series and comparative studies with major biases (level of evidence 4).

EA Expert agreement
In the absence of studies, the recommendations are based on the agreement of experts in the working group, after consultation with the review group. If no grade has been assigned, this does not mean that the recommendations are not relevant or useful. However, this should prompt further studies.

4. Pre-treatment assessment

4.1. Screening for another cause of liver disease
Other causes of chronic liver disease or factors exacerbating the natural course of hepatitis C should be investigated. HBV and HIV serology should be carried out in all patients. Alcohol use should be assessed and appropriate management set in place in the event of at-risk use. Comorbidities (autoimmunity, metabolic disease, diabetes, excessive weight or obesity, dyslipidaemia, etc.) should be assessed and managed.

Full information on the medication taken by the patient should be obtained, both for physician-prescribed medication and also over-the-counter products. Specialist opinions should be sought for severe comorbidities requiring specific treatment.

4.2. Assessment of the severity of hepatitis C

4.2.1. Assessment of liver fibrosis
Pre-treatment assessment of liver disease is essential as it determines the patient's prognosis and modifies their therapeutic management.

The initial work-up should investigate for all other causes of chronic liver disease (alcohol, metabolic syndrome, HBV, haemochromatosis, autoimmune hepatitis, chronic cholestatic disorders, etc.).
The severity of liver disease should be routinely assessed in order to diagnose cirrhosis. Non-invasive methods for the diagnosis of liver fibrosis recommended by the French National Authority for Health (HAS) should be used: measurement of liver stiffness by FibroScan or a blood test (FibroTest, FibroMeter, Hepascor). Although cirrhosis is clinically apparent, non-invasive methods have prognostic value (2, 3). Due to the efficacy and limited number of undesirable effects arising from direct-acting antivirals, liver biopsy (LB) is not recommended in hepatitis C unless the indication for LB is not directly related to HCV. It does not seem ethical to expose a patient with discordance between two non-invasive results to the risk of LB, when highly effective risk-free treatment is available.

The prognosis for hepatitis C can be assessed by non-invasive diagnostic methods for liver fibrosis. The prognosis may guide the choice as to whether the patient requires treatment or not. AFEF expert opinions on the non-invasive assessment of the severity of liver disease are available online at the AFEF website (www.afef.asso.fr) and are regularly updated in line with the latest knowledge.

When monitoring without treatment is instituted, non-invasive methods for liver fibrosis assessment should be carried out every year. In patients with a liver stiffness score below 7 kPa, the prognosis is excellent and annual monitoring is sufficient (3). In patients with a liver stiffness score between 7 and 14 kPa and a change in the liver stiffness score < 1 kPa in 3 years, the prognosis is excellent, even without treatment. However, if the change in the liver stiffness score is > 1 kPa in 3 years, the patient should be treated promptly (3). By extrapolation, a (confirmed) increase of more than 1 kPa in the course of a year is a strong incentive to treat the patient promptly.

In the event of cirrhosis, six-monthly screening for hepatocellular carcinoma by abdominal ultrasonography is essential. An AFEF expert opinion on the limit values for the non-invasive methods to be used for screening of hepatocellular carcinoma will be uploaded shortly to the AFEF website (www.afef.asso.fr) and will be regularly updated in line with the latest knowledge.
RECOMMENDATIONS

1. Pre-therapeutic assessment should investigate for all other causes of chronic liver disease (A)
2. Full, detailed information on the medication taken by the patient should be obtained (A)
3. The presence or absence of cirrhosis should be diagnosed during the management of chronic hepatitis C (A)
4. Liver biopsy is not recommended in chronic hepatitis C virus infection without any comorbidities, irrespective of the outcome of non-invasive methods for the diagnosis of liver fibrosis (EA)
5. In case of discordant results between non-invasive methods, the most severe outcome should be taken into account (EA)
6. In the absence of treatment, patients should be monitored yearly with a non-invasive method for the diagnosis of liver fibrosis (EA)
7. In the absence of treatment, it is recommended that patients be monitored by means of a once yearly appointment, so that they can receive treatment as soon as this is indicated (EA)
8. Six-monthly screening for hepatocellular carcinoma by abdominal ultrasonography is essential in all patients with severe fibrosis and cirrhosis (A)
8. Endoscopic screening for oesophageal varices is recommended in patients with cirrhosis (A)

4.2.2. Factors associated with liver fibrosis progression

Numerous exacerbating factors for liver fibrosis exist (Table 1). These should be assessed during patient management: age, male gender, alcohol and/or cannabis use, metabolic syndrome (excessive weight or obesity, diabetes, hypertension, dyslipidaemia), coinfection with HIV or HBV, genotype 3 (4, 5).

Alcohol use must be routinely assessed during patient management (6). For this purpose, questionnaires suitable for the diagnosis of misuse may be used (AUDIT, CAGE, DSM-V). Excessive alcohol use is defined in accordance with WHO criteria: more than 21 units a week for males and more than 14 units a week for females, or more than 6 units on a single occasion. Alcohol-dependent patients should be referred to an addiction specialist. In the event of metabolic syndrome, complementary care should be defined and proposed (dietetic, diabetes, cardiology appointments, etc.).
Table 1. Factors associated with the progression of liver fibrosis.

<table>
<thead>
<tr>
<th>Host</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>Genotype 3</td>
</tr>
<tr>
<td>Age at contamination</td>
<td>Coinfection with HBV or HIV</td>
</tr>
<tr>
<td>Intrahepatic inflammation</td>
<td></td>
</tr>
<tr>
<td>Stage of fibrosis</td>
<td></td>
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<tr>
<td>Organ transplantation</td>
<td></td>
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<tr>
<td>Alcohol use</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

RECOMMENDATIONS

1. Comorbidities are an exacerbating factor for the progression of liver fibrosis (A)
2. Comorbidities associated with hepatitis C virus infection (alcohol use, excessive weight, diabetes, dyslipidaemia and coinfection with other viruses) should be assessed and managed (A)

4.3. Assessment of the non-hepatic severity of hepatitis C

4.3.1. Extrahepatic manifestations

Numerous extrahepatic manifestations are associated with hepatitis C virus infection (7). The production of mixed cryoglobulins in the blood is the most common extrahepatic manifestation associated with HCV. However, this abnormal laboratory finding (positive test for cryoglobulin) should not be confused with the clinical signs of cryoglobulinaemic vasculitis. The majority of patients with mixed cryoglobulinaemia are clinically asymptomatic; however, a quarter of these patients may present symptoms the underlying anatomical foundation of which involves vasculitis of the small vessels. Mixed cryoglobulinaemia syndrome is characterised by the clinical triad of purpura-arthralgia-asthenia. Several other types of organ involvement may occur, particularly affecting the peripheral nervous system (sensorimotor polyneuropathy and, more rarely, sensorimotor or sensory multiple mononeuropathy), the kidneys (membranoproliferative glomerulonephritis), or indeed the central nervous system. The treatment of hepatitis C is often able to cure clinical symptoms related to cryoglobulinaemia (8).
Cryoglobulinaemic glomerulonephritis is a membranoproliferative glomerular nephropathy, which progresses in a chronic manner interspersed with acute episodes. Alongside cryoglobulinaemic vasculitis which preferentially affects small-calibre vessels, there are authentic findings on vasculitis affecting medium-calibre vessels, such as polyarteritis nodosa.

Although dry mouth and/or eye syndrome is often observed in patients with chronic HCV infection, combination of HCV and Sjögren's syndrome is very rare. Numerous studies have demonstrated an increase in the prevalence of HCV infection in the course of haematological malignancies, particularly B-cell non-Hodgkin's lymphoma (NHL). Porphyria cutanea tarda (PCT) is a rare disease characterised by abnormal porphyrin metabolism, related to uroporphyrinogen-decarboxylase enzyme deficiency. Several studies on prevalence have demonstrated the presence of anti-HCV antibodies in the serum of patients presenting sporadic forms of PCT.

Numerous autoantibodies are found in HCV-infected patients. Rheumatoid factor is the most frequently detected; however, other autoantibodies are frequently observed: antinuclear antibodies, anti-smooth muscle antibodies, anti-thyroglobulin antibodies, anti-cardiolipin antibodies, anti-endothelial cell antibodies, anti-thyroid antibodies and anti-LKM1 antibodies.

Hepatitis C virus infection is often associated with extrahepatic manifestations which vary in severity. Curing hepatitis C generally leads to resolution of symptoms if treatment is started early. However, the efficacy of direct-acting antivirals on the resolution of the extrahepatic manifestations of hepatitis C has not yet been determined.

The prevalence of fatigue fluctuates according to the chosen criteria; however, certain patients describe severe fatigue (severely impacting upon their social and professional activities). The main risk factors are female gender, age over 50 years, and the presence of cirrhosis, depression, arthralgia, myalgia and purpura. Furthermore, fatigue is the main factor which reduces patient quality of life (9).

**RECOMMENDATIONS**

1. The extrahepatic manifestations of hepatitis C should be investigated and managed (A)
2. Incapacitating asthenia is an extrahepatic manifestation of hepatitis C (A)
3. In these patients, the treatment of hepatitis C is the same as for patients without extrahepatic manifestations (EA)
4. Early treatment of hepatitis C is recommended in order to increase the chances of these extrahepatic manifestations disappearing (EA)
4.3.2. Patient health status
Evaluation of disease severity may also be carried out by means of a patient health status assessment performed by the patient him/herself (PRO: patient reported outcomes). Patient-reported outcomes notably take physical and mental quality of life into account (10). This new endpoint has been studied during treatment with new direct-acting antiviral agents. SVR was shown to be associated with an improvement in "PRO" (11).

4.4. Virological assessment
Quantification of HCV RNA is indicated in patients who require treatment. Quantification should be performed by means of a sensitive test and the results should be expressed in IU/ml. Determination of HCV genotype (and sub-types) is essential before initiating treatment.

RECOMMENDATIONS

1. Determination of HCV genotype and quantification of HCV viral load are essential before initiating treatment (A)
2. In the absence of treatment, HCV viral load does not need to be monitored (A)

5. Indications for the treatment of chronic hepatitis C virus infection
Antiviral treatment should be proposed for all patients with chronic hepatitis C, whether treatment-naive or for whom previous treatment has failed, with compensated or decompensated liver disease, excluding those presenting a severe extrahepatic comorbidity limiting their short-term life expectancy. However, not all patients suffering from chronic hepatitis C can have immediate access to antiviral treatment, owing to human, organisation and budgetary constraints, hence priority for access to antiviral treatment should be determined (Table 2). Universal access to treatment is a short-term objective with the aim of eradicating the hepatitis C epidemic by 2025. This will require gradual extension of the indications for treatment based on a time-frame to be established with the health authorities.
The first step has been to prioritise access to antiviral treatment according to severity of fibrosis, the risk of progression to more advanced disease and the presence of severe extrahepatic manifestations related to HCV.

Based on this prioritisation approach, treatment should be proposed to patients with at least moderate fibrosis (F2 or F3 or F4 according to METAVIR score). Sustained virological response (SVR) is associated with a reduction in the onset of liver disease complications, particularly hepatocellular carcinoma (HCC), and with an improvement in survival. Two recent meta-analyses thus confirmed that viral eradication reduced the risk of developing HCC by a factor of 3 to 5 (12, 13). A multicentre international study describing the long-term follow-up of 530 patients originating from 5 European and Canadian centres (14) also identified a benefit in terms of overall mortality, related to liver disease or not, after HCV eradication. The cumulative incidence of mortality secondary to liver disease at 10 years was 1.9% in patients with SVR versus 27.4% among patients not having achieved viral eradication. After SVR, at 10 years, only 5.1% of patients developed HCC and 2.1% liver failure. The reversibility of cirrhosis, after SVR, has been documented in several studies and seems to be associated with the absence of onset of medium-term complications (15). Antiviral treatment should also be proposed for patients with compensated or decompensated cirrhosis. Interferon is contraindicated in these patients owing to the major risk of onset of severe complications, particularly infection, during treatment (16) (17). These patients should be treated with therapeutic regimens not containing pegylated interferon. HCV eradication rapidly and significantly improves Child Pugh and MELD scores, and reduces the incidence of complications (18). However, the improvement in terms of clinical and laboratory parameters observed in patients with Child Pugh scores > 12 and/or MELD scores >20 remains limited. In this case, treatment should be provided in close consultation with a liver transplantation team. Exacerbation of liver disease, attributed to the natural course of the disease, has in fact been observed in some of these patients; however, additional data are necessary in order to rule out the responsibility of antiviral treatment. Hence, initiation of antiviral treatment in patients with decompensated liver disease should take place at centres experienced in this approach, while efficacy and safety data remain limited.

To summarise, viral eradication in patients with severe hepatic fibrosis leads to stabilisation, or, indeed, regression of fibrosis and prevents cirrhosis in F3 patients. At the cirrhosis stage, it reduces the risk of complications, particularly HCC, and the need for liver transplantation. Treatment of hepatitis C is thus a cost-effective therapeutic strategy in the mild to long term.

Treatment is recommended for patients with moderate fibrosis. The factors influencing the course of chronic hepatitis C have been widely studied and are mainly related to the host. Age in itself has a major impact as cirrhosis and the complications thereof are observed more frequently after the age of 60 years, irrespective of the age of contamination. The indication should take into account the rate of
progression of fibrosis, the patient’s physiological age and life expectancy associated with possible non-hepatic comorbidities (excessive alcohol use, metabolic syndrome).

The next step is to extend the indications, regardless of fibrosis stage, to:
- Patients with genotype 3 infection
- Patients with risk factors for exacerbation of liver disease
- Patients with extrahepatic manifestations (including incapacitating asthenia)
- Patients at high risk of transmitting HCV

Genotype 3 is currently the most difficult HCV to eradicate. There are only three agents with antiviral activity against this genotype, but the antiviral potency of these drugs is less than for other genotypes. This is evidenced by SVR rates below 90% in cirrhotic patients infected with genotype 3 who receive 24 weeks of a combination of sofosbuvir and daclatasvir with or without ribavirin (19), whereas in non-cirrhotic patients, administration of this combination for 12 weeks without ribavirin is associated with SVR rates of 92 to 97% (20). In patients with genotype 3 infection, antiviral treatment should therefore be initiated without waiting for the severe fibrosis or cirrhosis stage, i.e. from the moderate fibrosis stage, but also the mild fibrosis or no liver fibrosis stage.

Patients with comorbidities (excessive alcohol use and metabolic syndrome) have an increased risk of disease progression. The detrimental role of excessive, or even moderate, alcohol use on the rate of disease progression has been established (21). Several studies have shown that the existence of insulin resistance and/or metabolic steatohepatitis accelerated the progression of liver disease (22). Combination of metabolic steatohepatitis with chronic hepatitis C also increases the risk of HCC (23).

HCV-HIV coinfection was initially associated with faster progression of fibrosis in HCV-infected patients (24), increasing the risk of cirrhosis and HCC (25). This rapid progression was largely related to immunosuppression induced by chronic HIV infection (24) (26).

HCV-HBV coinfection is associated with accelerated progression of fibrosis (27). Furthermore, studies highlight the increased incidence of HCC in HBV-HCV coinfected patients (28).

Patients awaiting transplantation or organ transplant patients should have access to antiviral treatment regardless of the severity of hepatic fibrosis. Graft re-infection with HCV post-liver transplantation, a practically constant occurrence in patients with hepatitis C virus replication before transplantation, is responsible for severe liver disease. In certain rare forms of graft re-infection post-liver transplantation, the hepatitis C viral load may be very high and be associated with cholestatic fibrosing hepatitis with a very poor prognosis. The recent arrival of direct-acting antivirals has transformed the prognosis of this form of graft re-infection (29) (30). Other than cholestatic fibrosing hepatitis, the progression of hepatitis C virus infection in the graft is accelerated compared to immunocompetent patients, with a risk of cirrhosis ranging from 10 to 30% at 5 years according to the
series (31). In the event of cirrhosis, there is a high short-term risk of decompensation, with a mortality rate of 60% in the year following the first episode of decompensation. This progression necessitates further transplantation in approximately 10% of patients. In France, graft re-infection with HCV is the cause of a significant reduction (approximately 10%) in graft and patient survival relative to patients undergoing transplantation for other indications. The detrimental impact of HCV infection is also observed in other organ transplant patients. The incidence of HCV is approximately 7 times more common among kidney transplant patients infected with HCV than among non-infected patients (32). In this context, antiviral treatment is proposed more frequently at the chronic hepatitis stage in the liver graft. This strategy is probably now obsolete as antiviral treatments can be administered at an earlier stage due to better tolerability (33). The role of direct-acting antivirals as pre-emptive treatment should be studied, together with the cost-effectiveness ratio for this approach, compared to treatment in patients with established chronic graft re-infection. Very promising results have been reported with the combination of sofosbuvir and ribavirin administered up to liver transplantation (33). These indicate satisfactory tolerability of treatment and > 90% of patients with undetectable HCV RNA during treatment and at the time of liver transplantation associated with the absence of virus recurrence in approximately two-thirds of patients post-transplantation. This rate was even higher, in the region of 95%, in the sub-group of patients with complete viral suppression for more than one month before transplantation. In practice, antiviral treatment should be proposed before organ transplantation in order to prevent graft re-infection with HCV post-liver transplantation or exacerbation of hepatitis C after other organ transplantation. Antiviral treatment should be initiated shortly after transplantation, regardless of the organ transplanted, to avoid rapid progression of hepatitis C related to immunosuppression.

**Numerous extrahepatic manifestations** have been reported during chronic hepatitis C and patients with these disorders should have access to treatment. A clear relationship has been demonstrated between chronic hepatitis C and vasculitis related to cryoglobulinaemia, responsible for skin disorders (purpura), renal disorders, (glomerulonephritis), rheumatological disorders (polyarthritis), and neurological disorders (peripheral neuropathy) (1). Numerous other relationships with various diseases have been described (thyroid disorders, sicca syndrome, lichen planus, porphyria cutanea tarda, lymphocytic sialadenitis, B-cell non-Hodgkin lymphoma) although the causal relationship between HCV infection and these diseases is not always clearly established. Patients suffering from vasculitis associated with cryoglobulinaemia, immune complex nephropathy, B-cell non-Hodgkin lymphoma, and neuropathy should receive antiviral treatment regardless of the severity of liver disease.

**Incapacitating asthenia** is an extrahepatic manifestation more frequently observed in patients with chronic hepatitis C than in patients not infected with HCV (34). The mechanisms involved in this manifestation is more than likely diverse and has not yet been widely documented. Patients with
incapacitating fatigue should receive antiviral treatment regardless of the severity of liver disease. A new assessment of the severity of liver disease is the patient reported outcome. This health status assessment takes physical and mental quality of life into account. Patients with SVR have an improvement in quality of life (35).

Patients at risk of transmitting HCV are active intravenous drug users, homosexual males involved in at-risk sexual practices, women who wish to conceive, patients on haemodialysis, patients living in an institution and prisoners. One of the central elements for preventing the spread of HCV among drug users is the treatment of infected subjects (1) (36). In the context of current major therapeutic progress, the reduction in the number of infected individuals owing to this treatment is a major factor for future prevention, which has already been the case for HIV infection. The modelling studies (37) show that a marked reduction in the prevalence of hepatitis C may be obtained by treating infected drug users (preventive treatment) although the modelling results based on the impact of opioid substitution therapy and syringe exchange programmes were much more limited (38). Sexual transmission of HCV is rare; according to a recent study, the rate of transmission among heterosexual couples claiming to be monogamous is 0.7% per year, equivalent to one case of transmission per 190,000 instances of sexual intercourse. Traumatic intercourse and unprotected sexual intercourse during menstrual periods should, however, be avoided. Sexual transmission of HCV has mainly been reported among HIV-infected homosexual males. Antiviral treatment may be recommended among active drug users and homosexual males to prevent the transmission of HCV. This cannot be achieved without targeted interventions in terms of prevention within these communities to inform them of the risks of re-infection after eradication of the virus, together with the essential preventive measures to be implemented. C.

The prevalence of hepatitis C in French prisons was estimated at 4.8% in 2010. The risk of contamination during incarceration is probably high due to the high rate of high-risk practices (drug use, equipment-sharing, home tattoos, etc.). In this population, educational efforts on the risk factors for contamination should be broadly intensified and treatment should be routinely proposed, for the individual benefit of the patient, and the collective value in reducing the reservoir of contamination. Certain individuals should also benefit from priority treatment, regardless of disease stage, as they are at risk of transmitting infection. These are healthcare professionals or women wishing to conceive.

The third step is universal treatment.

This step will make it possible to treat all patients who have not yet been able to benefit from antiviral treatment, but also newly diagnosed patients.

Treatment is not recommended for patients with limited short-term life expectancy, related to extrahepatic comorbidities.
RECOMMENDATIONS

ACCESS TO UNIVERSAL TREATMENT IS A SHORT-TERM OBJECTIVE

1. All patients should be assessed for treatment with direct-acting antiviral agents (A)
2. Treatment is recommended for patients with moderate or severe fibrosis, or cirrhosis (A)
3. Treatment is recommended regardless of fibrosis stage in patients (A):
   - with genotype 3 infection
   - with comorbidities (excessive alcohol use, metabolic syndrome)
   - coinfected with HIV or HBV
   - awaiting transplantation or post-organ transplantation
   - with a significant extrahepatic manifestation related to HCV: vasculitis related to cryoglobulinaemia, nephropathy related to HCV, B-cell non-Hodgkin lymphoma
   - with incapacitating fatigue
4. Treatment is recommended regardless of fibrosis stage in patients at risk of transmitting HCV (A)
   - parenteral and nasal drug users
   - MSM involved in at-risk practices
   - women wishing to conceive
   - healthcare professionals
   - patients on haemodialysis
   - patients who are in prison
   - patients living in an institution
5. In the short-term, universal treatment should be incorporated into general management: screening, management of comorbidities, prevention of recontamination (A)

RECOMMENDATIONS

1. Treatment is not recommended for patients with limited short-term life expectancy (A)
### Table 2. Indications for the treatment of chronic hepatitis C in 2015.

<table>
<thead>
<tr>
<th>Antiviral treatment</th>
<th>Patient group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment indicated</td>
<td>All patients with chronic hepatitis C</td>
</tr>
<tr>
<td>Treatment recommended according to hepatic fibrosis</td>
<td>Patients with moderate or severe fibrosis, or compensated or decompensated cirrhosis</td>
</tr>
</tbody>
</table>
| Treatment recommended regardless of the stage of hepatic fibrosis | Patients with HIV coinfection  
Patients with HBV coinfection  
Patients with genotype 3 infection  
Patients with comorbidities: excessive alcohol use, metabolic syndrome  
Patients for whom organ transplantation is indicated  
Patients having undergone organ transplantation  
Patients with an extrahepatic manifestation  
Patients with incapacitating fatigue |
| Treatment recommended due to the risk of transmission of HCV | Active parenteral and nasal drug users  
MSM  
Women wishing to conceive  
Haemodialysis patients  
Patients who are in prison  
Patients living in an institution  
Healthcare professionals |
| Universal treatment recommended in the short term | Patients not yet receiving treatment  
Newly diagnosed patients |
| No access to treatment                     | Patients with limited life expectancy in the short term                       |
6. Drugs for hepatitis C

The three main therapeutic classes for hepatitis C are protease inhibitors, NS5A inhibitors and NS5B inhibitors.

The medicinal products for hepatitis C are shown in Tables 3 and 4. The interactions between direct-acting antiviral agents and antiretrovirals are described in the section on HCV-HIV coinfection.

Table 3. Drugs for hepatitis C.

<table>
<thead>
<tr>
<th>Therapeutic classes</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS3/4A protease inhibitors</td>
<td>Simeprevir</td>
</tr>
<tr>
<td></td>
<td>Asunaprevir</td>
</tr>
<tr>
<td></td>
<td>Vaniprevir</td>
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<td></td>
<td>Sovaprevir</td>
</tr>
<tr>
<td></td>
<td>Vedroprevir</td>
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<tr>
<td></td>
<td>Paritaprevir/ritonavir</td>
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<tr>
<td></td>
<td>Grazoprevir</td>
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<td></td>
<td>GS-9857</td>
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<td></td>
<td>ABT-493</td>
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<tr>
<td>NS5A inhibitors</td>
<td>Daclatasvir</td>
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<td></td>
<td>Ledipasvir</td>
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<td></td>
<td>Samatasvir</td>
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<td></td>
<td>Ombitasvir</td>
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<td>Elbasvir</td>
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<td>GS-5816</td>
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<td>ACH-3102</td>
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<td>PPI-668</td>
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<td>MK-8408</td>
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<td>ABT-530</td>
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<tr>
<td>NS5B inhibitors</td>
<td>Sofosbuvir</td>
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<tr>
<td>Nucleoside or nucleotide</td>
<td>VX-135</td>
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<tr>
<td></td>
<td>IDX20963</td>
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<td></td>
<td>ACH-3422</td>
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<td>MK-3682</td>
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<tr>
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<td>Dasabuvir</td>
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<td>Lomibuvir</td>
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<td></td>
<td>Setrobuvir</td>
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<td>Deleobuvir</td>
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<td>PPI-383</td>
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<td>GS-9669</td>
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<td>BMS-791325</td>
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</tbody>
</table>
**Table 4. Presentation and dosage of HCV drugs.**

<table>
<thead>
<tr>
<th>Medicinal products</th>
<th>Presentation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>Tablets containing 200 or 400 mg</td>
<td>1000 mg/day if weight &lt; 75 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1200 mg/day if weight ≥ 75 kg</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi®)</td>
<td>Tablets containing 400 mg</td>
<td>1 tablet per day</td>
</tr>
<tr>
<td>Simeprevir (Olysio®)</td>
<td>Tablets containing 150 mg</td>
<td>1 hard capsule per day</td>
</tr>
<tr>
<td>Daclatasvir (Daklinza®)</td>
<td>Tablets containing 30, 60 or 90 mg</td>
<td>1 tablet per day</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir (Harvoni®)</td>
<td>Tablets containing sofosbuvir 400 mg and ledipasvir 90 mg</td>
<td>1 tablet per day</td>
</tr>
<tr>
<td>Dasabuvir (Exviera®)</td>
<td>Tablets containing 250 mg</td>
<td>1 tablet morning and evening</td>
</tr>
<tr>
<td>Paritaprevir/ritonavir + ombitasvir (Viekirax®)</td>
<td>Tablets containing paritaprevir 75 mg, ritonavir 50 mg and ombitasvir 12.5 mg</td>
<td>2 tablets once a day</td>
</tr>
<tr>
<td>Grazoprevir + elbasvir</td>
<td>Tablets containing grazoprevir 100 mg and elbasvir 10 mg</td>
<td>1 tablet per day</td>
</tr>
</tbody>
</table>

**Sofosbuvir** is eliminated via the kidneys (80%) and in the stools (15%). Urinary sofosbuvir predominantly consists of its nucleoside metabolite GS-331007 (78%). This means that renal clearance is the main route of elimination of sofosbuvir GS-331007. To date, no dose recommendations can be issued for sofosbuvir in patients with severe renal impairment (glomerular filtration < 30 ml/min/1.73 m²). The main undesirable effects of sofosbuvir in combination with ribavirin (> 20%) are asthenia and headache.

Sofosbuvir is not metabolised by cytochrome P450, but is transported by protein P-gp (P-glycoprotein). Medicinal products that are potent P-gp inducers significantly decrease sofosbuvir plasma concentration and could therefore reduce the efficacy of sofosbuvir. Hence, sofosbuvir should not be administered with G-gp inducers such as rifampicin, carbamazepine, or phenytoin; interactions are also observed with rifabutin, rifapentine and modafinil. Administration of amiodarone (and possibly also dronedarone) with sofosbuvir in combination with daclatasvir, simeprevir or ledipasvir is contraindicated due to the risk of severe bradycardia. The mechanism behind this interaction is not known.
**Simeprevir** is extensively bound to plasma proteins (> 99.9%), primarily to albumin. Simeprevir is metabolised by the hepatic CYP3A system. It is mainly eliminated in the bile. The AUC of simeprevir is 2 to 4-fold higher in patients with Child B cirrhosis and 5.2-fold higher in patients with Child C cirrhosis. No dose adjustment of simeprevir is required in patients with renal impairment. Co-administration of simeprevir with CYP3A4 inhibitors or inducers is not recommended. The medicinal products contraindicated with simeprevir are anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), certain antibiotics (rifampicin, rifabutin, rifapentine), antifungals (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole), systemic dexamethasone, cisapride and numerous antiretrovirals. Dose adjustments are required with certain antiarrhythmics, warfarin, calcium channel blockers, HMG Co-A reductase inhibitors and anxiolytics. No dose adjustment is required with tacrolimus or sirolimus. However, co-administration of simeprevir with ciclosporin is not recommended as this leads to increased simeprevir plasma levels.

**Daclatasvir** is 90% eliminated in the stools, and less than 10% is eliminated in the urine. Exposure to daclatasvir is reduced in patients with cirrhosis (regardless of Child score). However, no dose adjustment is required. Compared to subjects with normal renal function, daclatasvir AUC is 18%, 39% and 51% higher for subjects with creatinine clearance values of 60, 30 and 15 ml/min, respectively. In haemodialysis patients, daclatasvir AUC is increased by 20%. No dose adjustment is required for daclatasvir in patients with renal impairment. Daclatasvir is a substrate of CYP3A4 and a substrate and inhibitor of P-gp. It is also an inhibitor of OATP1B1 and BCRP. Co-administration of daclatasvir with medicinal products which induce CYP3A4 and P-gp (thus reducing the daclatasvir concentration) is contraindicated. Hence, the dose of daclatasvir should be adjusted during co-administration with anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital), certain antibiotics (rifampicin, rifabutin, rifapentine), and systemic dexamethasone. The dose of daclatasvir should be reduced to 30 mg/day in the presence of clarithromycin, telithromycin, erythromycin, ketoconazole, itraconazole, posaconazole and voriconazole.

**Ledipasvir** is mainly eliminated via the biliary route, in the unchanged form of ledipasvir. The median half-lives of sofosbuvir and its main metabolite (GS-331007) following administration of sofosbuvir + ledipasvir are 0.5 and 27 hours, respectively. Ledipasvir plasma exposure (AUC) is identical in control patients and in subjects with severe hepatic impairment. No dose adjustment is required for patients with mild or moderate renal impairment. However, the safety of the combination sofosbuvir + ledipasvir has not been assessed in patients with severe renal impairment.
impairment (eGFR < 30 ml/min/1.73m²) or patients requiring haemodialysis. The main undesirable effects of the combination sofosbuvir + ledipasvir are asthenia and headache.

The drug interactions described for sofosbuvir are also described for the combination sofosbuvir + ledipasvir. The transporters of this combination are P-gp and BCRP (Breast Cancer Resistant Protein). Co-administration of medicinal that inhibit P-gp and/or BCRP could increase exposure to sofosbuvir and to ledipasvir, with, however, a lesser clinical impact. However, caution is required with substrates of P-gp such as digoxin and dabigatran, and also other medicinal products transported by these proteins (amlodipine, buprenorphine, carvedilol, ciclosporin). Co-administration of amiodarone is contraindicated owing to the risk of bradycardia. The use of rosuvastatin is not recommended and interactions with other statins cannot be ruled out. Ledipasvir solubility decreases as pH increases. Medicinal products that increase gastric pH could therefore decrease ledipasvir concentration. Anti-H2 or proton pump inhibitors should therefore be taken either at the same time as ledipasvir or 12 hours later.

**Paritaprevir** is mainly metabolised by CYP3A4 and is combined with a low dose of ritonavir (booster). It is mainly excreted in the stools. **Ombitasvir** is also eliminated in the stools. **Dasabuvir** is metabolised in the liver, and its main metabolite is eliminated via the biliary route and in the stools. In patients with Child C cirrhosis, paritaprevir AUC is increased 9.5-fold, ombitasvir AUC is decreased by 54%, whereas dasabuvir AUC is increased 3.3-fold. No dose adjustment is required in patients with Child A or Child B cirrhosis. However, this combination is contraindicated in patients with Child C cirrhosis. In patients with severe renal impairment (creatinine clearance < 30 ml/min), paritaprevir AUC is increased by 45%, ritonavir AUC by 114% and dasabuvir AUC by 50%. However, no dose adjustment is required in these cases. Paritaprevir is mainly metabolised by CYP3A4, dasabuvir is metabolised by CYP2C8, and ombitasvir is hydrolysed. However, ombitasvir and dasabuvir may be metabolised by CYP3A4. Paritaprevir inhibits OATP1B1/B3, P-gp and BCRP. Dasabuvir and ritonavir could inhibit P-gp and BCRP. Hence, numerous potential drug interactions are possible. Ritonavir is a potent inhibitor of CYP3A4. Therefore, co-administration with medicinal products metabolised by this enzyme could increase their plasma concentration. Numerous medicinal products are contraindicated: alfuzosin, amiodarone, astemizole, terfenadine, cisapride, ergot alkaloids, lovastatin, simvastatin, atorvastatin, midazolam, triazolam, quetiapine, quinidine, salmeterol, sildenafil, carbamazepine, phenytoin, phenobarbital, rifampicin, enzalutamide, antifungals and macrolides. In addition to these contraindications, numerous other medicinal products should be used with caution, particularly antiretrovirals (see section on HCV-HIV coinfection).
**Grazoprevir** (100 mg) is combined with **elbasvir** (50 mg) in the form of a once daily tablet. Grazoprevir is a substrate of CYP3A4, P-gp and OATP1B1, and an inhibitor of CYP2C8, 3A4 and UGT1A1. Elbasvir is a substrate of CYP3A4, P-gp and OATP. No dose adjustment is required in patients with Child B or C cirrhosis.

### 7. Treatment according to HCV genotype

The main obstacle to interferon-based therapies is the risk of side-effects at a time when patients can be treated using other agents with significantly better tolerability and efficacy. The objectives relating to improved therapeutic efficacy and fewer side-effects are the reasons why the first-line use of interferon in combined treatments for hepatitis C virus has been abandoned. The proposed therapeutic options are indicated in chronological order according to the availability of the different agents in France and are summarised in Appendix 2. **With the same level of evidence, therapeutic regimens with SVR rates above 90% have been prioritised in the recommendations.** However, the results of cohort studies or therapeutic trials will be published shortly and taken into account in the updated AFEF recommendations in 2016.

#### RECOMMENDATIONS

1. Treatment comprising pegylated interferon is no longer recommended in patients with genotype 1, 2, 4, 5 and 6 (A)

#### RECOMMENDATIONS

1. In genotype 3 patients, pegylated interferon may be recommended in certain specific situations (A)
7.1 Treatment of genotype 1 patients

7.1.1. Treatment-naive genotype 1 patients

Several therapeutic regimens have been evaluated, the outcomes of which are shown in Table 5. These regimens generally comprise 12 weeks of treatment. In certain specific cases, treatment may last 24 weeks. Due to the difficulty in defining the target population, 8-week therapeutic regimens have not been adopted. In other cases, the addition of ribavirin may improve SVR rate. Eight options without interferon are available for the treatment of treatment-naive patients infected with genotype 1:

- Sofosbuvir + ribavirin for 24 weeks
- Sofosbuvir + simeprevir for 12 weeks
- Sofosbuvir + daclatasvir ± ribavirin for 12 weeks.
- Sofosbuvir + ledipasvir for 12 weeks
- Paritaprevir/ritonavir + ombitasvir + dasabuvir ± ribavirin for 12 or 24 weeks

Other combinations are currently in development

- Grazoprevir + elbasvir for 12 to 18 weeks
- Daclatasvir + asunaprevir + beclabuvir for 12 weeks.
- Sofosbuvir + GS-5816 for 12 weeks

**Genotype 1, treatment-naive, option 1**

Treatment-naive patients infected with HCV genotype 1 may be treated with sofosbuvir + ribavirin for 24 weeks.

**Comments**

In the study of Osinusi *et al.*, in 10 treatment-naive patients infected with genotype 1, and presenting no to moderate fibrosis lesions, SVR after 24 weeks of sofosbuvir + ribavirin was 90% (39). In 50 treatment-naive patients presenting severe fibrosis lesions (72% infected with sub-type 1a and 26% of fibrosis lesions F3-4 as per the Knodell score), SVR was only 68% among patients having received ribavirin doses adjusted to weight and 48% among those having received ribavirin 400 mg/day. Sub-type was not a predictive factor for SVR12 unlike non-existent to moderate fibrosis lesions.

In the study of Gane *et al.*, 25 non-cirrhotic treatment-naive patients infected with genotype 1 (88% with sub-type 1a) were treated with sofosbuvir + ribavirin for 24 weeks with a SVR rate of 84%, without sub-type having a predictive role in this limited sample size (40).

Option 1 is not recommended for SVR < 90%.
Genotype 1, treatment-naive, option 2

Treatment-naive patients infected with HCV genotype 1 may be treated with sofosbuvir + simeprevir ± ribavirin for 12 weeks.

Comments

In the COSMOS (phase 2) study, 39 patients (with severe fibrosis lesions F3-4) received treatment for 12 weeks with sofosbuvir + simeprevir (n = 7), 12 weeks with sofosbuvir + simeprevir + ribavirin (n = 12), 24 weeks with sofosbuvir + simeprevir (n = 8), or 24 weeks with sofosbuvir + simeprevir + ribavirin (n = 13) (41). SVR was 95%, without any influence arising from treatment duration, the presence or absence of ribavirin, or viral sub-type 1a or 1b (SVR12 not described in detail in the article). The overall study population (treatment-naive patients and non-responders) included 130 patients infected with sub-type 1a, 58 of whom had a Q80K mutation. In these cases, SVR was 88% versus 94% in patients without a mutation.

In the TRIO study, 822 patients were included and treated with combinations comprising simeprevir. Among the 301 treatment-naive patients infected with genotype 1, SVR was 83% with the combination sofosbuvir + simeprevir + ribavirin. In this study, the absence of cirrhosis was a factor associated with SVR (88% among non-cirrhotic patients versus 75% among cirrhotic patients) (42).

In the TARGET study, among the 303 patients infected with genotype 1 and evaluable for SVR4, this was 87% when the combination sofosbuvir + simeprevir was used without ribavirin and 89% with ribavirin, confirming the results of the phase 3 studies. Lastly, there was no significant difference between cirrhotic and non-cirrhotic patients, and no difference between patients with or without ribavirin (43).

In the OPTIMIST-1 study, 310 non-cirrhotic patients infected with genotype 1 (70% of whom were treatment-naive patients) received treatment for either 12 or 8 weeks after randomisation with stratification by genotype, previous treatment and IL28-B genotype. SVR was 97% and 83% in the arms treated for 12 and 8 weeks respectively, suggesting that the minimum required treatment duration is 12 weeks (44). In the OPTIMIST-2 study, 103 cirrhotic patients (49% treatment-naive patients and 70% genotype 1a patients) received treatment with sofosbuvir + simeprevir for 12 weeks. The overall SVR was 88% among treatment-naive patients (45).

Option 2 is not recommended for SVR < 90%, among genotype 1a patients or in genotype 1b patients with cirrhosis.
Genotype 1, treatment-naive, option 3

Treatment-naive patients infected with HCV genotype 1 may be treated with sofosbuvir + daclatasvir ± ribavirin for 12 weeks.

Comments

In the open-label study of Sulkowski et al., 126 treatment-naive patients (including 17 with cirrhosis) received treatment with sofosbuvir + daclatasvir with or without ribavirin: 15 patients with 7 days of sofosbuvir, followed by 23 weeks of daclatasvir + sofosbuvir, 14 patients with 24 weeks of daclatasvir + sofosbuvir, 15 patients with 24 weeks of daclatasvir + sofosbuvir + ribavirin, 41 patients with 12 weeks of daclatasvir + sofosbuvir and 41 patients with 12 weeks of daclatasvir + sofosbuvir + ribavirin (46). SVR was 100% in patients without ribavirin and 99% in patients with ribavirin. These results are based on very small sample sizes and need to be verified on larger sample sizes.

In the cohort study ANRS CO22 Hepather, 409 patients infected with genotype 1 (50% infected with genotype 1a, 78% cirrhotic patients, 9% Child B and C patients, 75% patients for whom previous treatment has failed, treatment comprising first-generation protease inhibitors in 56% of patients) were treated with sofosbuvir + daclatasvir with or without ribavirin for 12 to 24 weeks. SVR was 100% in non-cirrhotic patients regardless of therapeutic regimen. In cirrhotic patients, SVR was 82%, 97%, 100% and 96% among patients respectively treated for 12 weeks without ribavirin, 12 weeks with ribavirin, 24 weeks without ribavirin and 24 weeks with ribavirin, suggesting an optimum therapeutic regimen of 12 weeks without ribavirin among non-cirrhotic patients, and an optimum therapeutic regimen among cirrhotic patients of either 12 weeks with ribavirin or 24 weeks without ribavirin (47).

Genotype 1, treatment-naive, option 4

Treatment-naive patients infected with HCV genotype 1 may be treated with sofosbuvir + ledipasvir for 12 weeks.

Comments

In the open-label phase 2 study, LONESTAR, 60 non-cirrhotic, treatment-naive patients, 88% of whom were infected with sub-type 1a, were randomised, after stratification by sub-type, to 3 groups treated for 8 weeks with sofosbuvir + ledipasvir, 8 weeks with sofosbuvir + ledipasvir + ribavirin, or 12 weeks with sofosbuvir + ledipasvir (48). The SVR rates were 95%, 100% and 95%, respectively, without the sub-type having a predictive role.

In the phase 3 ION-1 study in treatment-naive patients (including 16% with cirrhosis and 67% infected with genotype 1a), 865 patients were randomised with a ratio of 1:1:1:1 to 4 groups treated with this
combination: one group treated for 12 weeks without ribavirin, one group treated for 12 weeks with ribavirin, one group treated for 24 weeks without ribavirin and one group treated for 24 weeks with ribavirin (49). SVR was at least 97% (99%, 97%, 98% and 99%, respectively), without any influence arising from the presence of cirrhosis, viral sub-type, treatment duration or ribavirin use.

In the phase 3 ION-3 study, 647 treatment-naive and non-cirrhotic patients (80% infected with genotype 1a, 13% F3 among patients having had a liver biopsy) were randomised with a ratio of 1:1:1 to 3 groups, 2 treated for 8 weeks (without and with ribavirin) and the third treated for 12 weeks without ribavirin (50). SVR was comparable in the 3 groups, 94%, 93% and 95%, respectively, without any of the usual variables (fibrosis, treatment duration, viral sub-type) having a predictive role in terms of SVR. However, in the group treated for 8 weeks, some uncertainty remains in patients with a high viral load (the limit of which has yet to be defined) and concerning the risk of NS5A mutations.

In the study conducted by Reddy KR et al., 513 patients, including 161 treatment-naive and cirrhotic patients, were treated for 12 or 24 weeks with sofosbuvir + ledipasvir with or without ribavirin. The SVR rate was 96%, without any influence arising from treatment duration or combination with ribavirin (51).

In a real-life study in Germany, 45 patients (including 49% of patients with genotype 1a, 47% of patients with genotype 1b and 4% of patients with genotype 4, without cirrhosis and 4% F3, and all with viraemia < 6,000,000 IU/ml), SVR4 was 100% after 8 weeks of treatment with sofosbuvir + ledipasvir, suggesting that 8 weeks of this combination would suffice in non-cirrhotic, treatment-naive patients, with low baseline viraemia (52). This preliminary result requires additional studies in order for this treatment duration to be recommended.

**Genotype 1, treatment-naive, option 5**

Treatment-naive patients infected with HCV genotype 1 may be treated with paritaprevir/ritonavir + ombitasvir + dasabuvir ± ribavirin for 12 to 24 weeks.

**Comments**

In the multicentre, randomised, double-blind, placebo-controlled (phase 3) SAPPHIRE-1 study, 631 patients received treatment for 12 weeks with paritaprevir (150 mg), ritonavir (100 mg), ombitasvir (25 mg), dasabuvir (250 mg) and ribavirin (1000 to 1200 mg/day according to weight) (53). SVR was 96.2% in the group with ribavirin (95% and 98% in patients infected with genotype 1a and 1b, respectively), without any influence arising from fibrosis score or change in ribavirin dosage.
In the PEARL III and IV (phase 3) studies, 419 patients infected with genotype 1b (PEARL-III) and 305 patients infected with genotype 1a (PEARL-IV), all non-cirrhotic, were treated with 150 mg/day paritaprevir, 100 mg/day ritonavir, 25 mg/day ombitasvir, 250 mg bid dasabuvir and ribavirin or placebo (54). SVR was 99%, in PEARL III, without any influence arising from combination with ribavirin. In PEARL-IV, SVR was 97% in patients treated with ribavirin and 90% in patients treated without ribavirin, suggesting the utility of combination with ribavirin in patients infected with genotype 1a and treated with this combination, even in the absence of cirrhosis.

In the TURQUOISE II study (phase 3, conducted in cirrhotic patients) 380 patients (including 120 treatment-naive patients) were included and treated for 12 or 24 weeks with 150 mg paritaprevir, 100 mg ritonavir, 25 mg ombitasvir, 250 mg bid dasabuvir and ribavirin according to weight (1000 to 1200 mg/day) (55). SVR was 94% and 95% in patients treated for 12 and 24 weeks, respectively: 92% and 93% in patients infected with genotype 1a and 100% in patients infected with genotype 1b, in the groups treated for 12 and 24 weeks, respectively.

In the GIFT-1 (phase 3) study, 363 Japanese patients infected with genotype 1b were treated with paritaprevir/ritonavir + ombitasvir for 12 weeks. The 321 non-cirrhotic patients (two-thirds of whom were treatment-naive patients) were randomised to 2 arms (treatment versus placebo) for 12 weeks, and the 42 patients with compensated cirrhosis (a quarter of whom were treatment-naive patients) were treated under open-label conditions for 12 weeks. SVR was 96% in treatment-naive patients and in the absence of cirrhosis, and 90% in the presence of cirrhosis (56).

**Genotype 1, treatment-naive, option 6**

Treatment-naive patients infected with HCV genotype 1 may be treated with grazoprevir + elbasvir ± ribavirin for 12 weeks.

**Comments**

In cohort A of the phase 2 C-WORTHY study, 123 treatment-naive and cirrhotic patients (including 64% infected with sub-type 1a) were randomised to 4 arms (1:1:1:1) and treated using this combination with ribavirin for 12 weeks, without ribavirin for 12 weeks, with ribavirin for 18 weeks and without ribavirin for 18 weeks (57). SVR was 90%, 97%, 97% and 94%, respectively, without any influence arising from combination with ribavirin or sub-type 1a or 1b.

In another publication on C-WORTHY, all patients included in the study were treatment-naive, non-cirrhotic and infected with sub-type 1a in 72% of cases (58). They were treated with the combination
grazoprevir + elbasvir for 8 to 12 weeks with or without ribavirin. SVR was 80% (24/30) among patients infected with genotype 1a and treated for 8 weeks with ribavirin, 93% (79/85) among patients infected with genotype 1a or 1b and treated for 12 weeks with ribavirin, 98% (43/44) among patients infected with sub-type 1a or 1b and treated for 12 weeks without ribavirin, suggesting that the optimum treatment duration for this combination was 12 weeks, without ribavirin among these non-cirrhotic, treatment-naive patients. Sub-type 1a or 1b had no influence on SVR.

In the C-EDGE phase III study, 419 patients (91% of patients with genotype 1, 50% of whom were genotype 1a and 41% genotype 1b, 22% cirrhotic patients) were treated with grazoprevir + elbasvir for 12 weeks (316 patients from inclusion and 105 patients after 12 weeks of placebo). The results for the 316 patients in the first arm were as follows: overall SVR of 95%, 92% among patients with genotype 1a (n = 157) and 99% among patients with genotype 1 b (n = 131), without any influence arising from the presence or absence of cirrhosis (59).

In the C-SWIFT study, 61 non-cirrhotic patients (82% of patients with genotype 1a) were treated with grazoprevir + elbasvir (31 patients for 4 weeks and 30 patients for 8 weeks), together with 41 cirrhotic patients (20 patients for 6 weeks and 21 patients for 8 weeks). SVR was 33%, 87%, 80% and 94%, respectively, suggesting a minimum treatment duration of at least 8 weeks (60).

**Genotype 1, treatment-naive, option 7**

Treatment-naive patients infected with HCV genotype 1 may be treated with asunaprevir + daclatasvir + beclabuvir for 12 weeks.

**Comments**

In the open-label UNITY-1 (phase 3) study, 312 non-cirrhotic, treatment-naive patients (including 73% of patients infected with genotype 1a) were treated with the fixed-dose combination containing 30 mg daclatasvir, 200 mg asunaprevir and 75 mg beclabuvir, twice daily for 12 weeks (61). SVR was 92% (90% for genotype 1a and 98% for genotype 1b).

In the UNITY-2 (phase 3) study, 112 cirrhotic, treatment-naive patients were treated with this same combination without or with ribavirin (62). SVR was 93% and 98%, respectively.
Genotype 1, treatment-naive, option 8

Treatment-naive patients infected with HCV genotype 1 may be treated with sofosbuvir + GS-5816 for 12 weeks.

Comments
In part A of the study conducted by Tran T et al. (phase 2), 55 treatment-naive patients infected with genotype were treated, after randomisation, for 12 weeks with sofosbuvir + GS-5816, 25 or 100 mg/day, with SVR rates of 96% and 100%, respectively (63). In part B of the same study, 120 non-cirrhotic, treatment-naive patients were treated with 25 (n = 50) or 100 mg of GS-5816 (n = 200) with or without ribavirin for 8 weeks only. SVR ranged from 81% to 90% suggesting an optimum treatment duration of 12 weeks and the absence of benefit from treatment with 100 mg of GS-5816 vs. 25 mg/day and combination with ribavirin.
RECOMMENDATIONS

1. The following therapeutic options are recommended for genotype 1 non-cirrhotic, treatment-naive patients:
   - Sofosbuvir + simeprevir for 12 weeks for patients with genotype 1b (A)
   - Sofosbuvir + daclatasvir for 12 weeks (A)
   - Sofosbuvir + ledipasvir for 12 weeks (A)
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks for patients with genotype 1a (A)
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir for 12 weeks for patients with genotype 1b (A)

2. The following therapeutic options may be recommended for genotype 1 non-cirrhotic, treatment-naive patients:
   - Grazoprevir + elbasvir for 12 weeks (A)
   - Daclatasvir + asunaprevir + beclabuvir + ribavirin for 12 weeks for patients with genotype 1a (A)
   - Daclatasvir + asunaprevir + beclabuvir for 12 weeks for patients with genotype 1b (A)
   - Sofosbuvir + GS-5816 for 12 weeks (B)

3. The following therapeutic options are recommended for treatment-naive genotype 1 patients with compensated cirrhosis:
   - Sofosbuvir + daclatasvir + ribavirin for 12 weeks (C)
   - Sofosbuvir + daclatasvir for 24 weeks (A)
   - Sofosbuvir + ledipasvir + ribavirin for 12 weeks (A)
   - Sofosbuvir + ledipasvir for 24 weeks (A)
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks (A)

4. The following therapeutic options may be recommended for treatment-naive genotype 1 patients with compensated cirrhosis:
   - Grazoprevir + elbasvir + ribavirin for 12 weeks (A)
   - Daclatasvir + asunaprevir + beclabuvir + ribavirin for 12 weeks for patients with genotype 1a (A)
   - Daclatasvir + asunaprevir + beclabuvir for 12 weeks for patients with genotype 1b (A)
   - Sofosbuvir + GS-5816 for 12 weeks (B)
7.1.2. Treatment-experienced genotype 1 patients [pegylated interferon and ribavirin ± first-generation protease inhibitor (telaprevir or boceprevir)]

Several therapeutic regimens have been evaluated, the outcomes of which are shown in Table 6. These regimens generally comprise 12 weeks of treatment. In certain specific cases, treatment may last 24 weeks. In other cases, the addition of ribavirin may improve SVR rate. Four options without interferon are available for the treatment of patients infected with genotype 1:

- Sofosbuvir + simeprevir for 12 weeks
- Sofosbuvir + daclatasvir ± ribavirin for 12 weeks
- Sofosbuvir + ledipasvir for 12 weeks
- Paritaprevir/ritonavir + ombitasvir + dasabuvir ± ribavirin for 12 or 24 weeks

Three combinations are currently in development:

- Grazoprevir + elbasvir for 12 to 18 weeks
- Daclatasvir + asunaprevir + beclabuvir for 12 weeks
- Sofosbuvir + GS-5816 for 12 weeks

Genotype 1, previously treated, option 1

Patients infected with HCV genotype 1 for whom treatment with pegylated interferon + ribavirin has failed may be treated with sofosbuvir + simeprevir for 12 weeks.

Comments

In the COSMOS (phase 2) study, 128 patients (including 80 patients with fibrosis F0-2 and 47 with severe fibrosis F3/4) were randomised to 4 groups, 2 of which received 12 weeks of sofosbuvir + simeprevir ± ribavirin, while the other 2 groups received 24 weeks of sofosbuvir + simeprevir ± ribavirin (41). SVR was 91%, without any influence arising from treatment duration, the presence or absence of ribavirin, or sub-type 1a or 1b. The overall study population included 130 patients infected with genotype 1a, 58 of whom had a Q80K mutation. SVR was 88% in these patients and 94% in patients without this mutation.

In the TRIO cohort, SVR was 81% in patients treated with sofosbuvir + simeprevir + ribavirin (80% of patients had experienced treatment failure with pegylated interferon + ribavirin) (42). In the TARGET cohort, SVR4 was 85% with ribavirin and 86% without ribavirin, without any influence arising from the presence or absence of cirrhosis (43).

In the OPTIMIST-1 study, 30% of the 310 non-cirrhotic patients included (75% patients with genotype 1a) had experienced treatment failure with pegylated interferon + ribavirin. They were
treated with sofosbuvir + simeprevir for 12 and 8 weeks, with SVR of 97% and 83%, respectively, suggesting a minimum optimum treatment duration of 12 weeks (44).

In the OPTIMIST-2 study, 103 cirrhotic patients (including 51% non-responders to treatment with pegylated interferon + ribavirin and 70% of patients with genotype 1a) were treated with sofosbuvir + simeprevir for 12 weeks. SVR was 79% (45).

Option 1 is not recommended for SVR < 90%.

**Genotype 1, previously treated, option 2**

Patients infected with HCV genotype 1 for whom treatment with pegylated interferon + ribavirin ± first-generation protease inhibitor has failed may be treated with sofosbuvir + daclatasvir for 12 weeks.

**Comments**

In the open-label study conducted by Sulkowski et al., 41 patients for whom treatment including protease inhibitors had failed (boceprevir and telaprevir) (including 43% with an NS3 mutation) were treated for 12 to 24 weeks with sofosbuvir + daclatasvir without ribavirin (n = 20) and with ribavirin (n = 21) (46). SVR was 98%.

In the HEPATHER cohort, 306 patients infected with genotype 1, for whom treatment with pegylated interferon + ribavirin had failed (78% cirrhotic patients, 50% of patients with genotype 1a, 56% of patients for whom treatment including a first-generation protease inhibitor had failed) were treated with sofosbuvir + daclatasvir ± ribavirin for 12 to 24 weeks. SVR was 100% in non-cirrhotic patients regardless of therapeutic regimen. Among cirrhotic patients, SVR was 82%, 97%, 100% and 98% in patients treated for 12 weeks without and with ribavirin and in patients treated for 24 weeks without and with ribavirin, respectively. The factors associated with failure were short treatment duration, absence of ribavirin use, and presence of cirrhosis (47).

**Genotype 1, previously treated, option 3**

Patients infected with HCV genotype 1 for whom treatment with pegylated interferon + ribavirin ± first-generation protease inhibitor has failed may be treated with sofosbuvir + ledipasvir for 12 weeks.

**Comments**

In the phase 3 ION-2 study, 440 patients for whom previous treatment had failed (including 20% cirrhotic patients, 79% of patients infected with genotype 1a and 52% of patients having experienced treatment failure with a combination comprising telaprevir or boceprevir) were randomised to
4 groups (1:1:1:1) treated for 12 weeks with sofosbuvir + ledipasvir, 12 weeks with sofosbuvir + ledipasvir + ribavirin, 24 weeks with sofosbuvir + ledipasvir and 24 weeks with sofosbuvir + ledipasvir + ribavirin (64). SVR was 94%, 96%, 99% and 99%, respectively, without any influence arising from subtype, previous treatment or type of treatment failure. Among cirrhotic patients, SVR was significantly higher in patients treated for 24 weeks (95% and 100%, respectively, without and with ribavirin) versus 12 weeks (86% and 82%, respectively, without and with ribavirin, \( p = 0.007 \)). The absence of cirrhosis was the only predictive factor for SVR (92% versus 98%), suggesting the superiority of a long therapeutic regimen in cirrhotic patients for whom previous treatment has failed. In contrast, subtype did not have any influence on SVR.

In the study conducted by Reddy KR et al., the pooled results of the phase 2 and 3 studies in which the patients had been treated with sofosbuvir + ledipasvir ± ribavirin (513 patients including 352 cirrhotic patients for whom previous treatment had failed), SVR was 90%, 96%, 98% and 100% in patients treated for 12 weeks without ribavirin, 12 weeks with ribavirin, 24 weeks without ribavirin and 24 weeks with ribavirin, respectively (51). A treatment duration of 24 weeks and combination with ribavirin were factors associated with SVR among patients for whom previous treatment had failed. In a sub-group of 28 patients for whom previous treatment had failed, a platelet count < 75,000/mm² was a predictive factor for failure with this combination.

Dvory-Sobol H et al. analysed SVR in the ION 1, 2 and 3 studies, according to the presence or absence of mutations at inclusion (65). Among patients having an NS5A mutation immediately before treatment, SVR was 69% and 100%, respectively, if the patients were treated for 12 weeks or 24 weeks. This suggests the need for screening of these mutations in patients having already been exposed to NS5A inhibitors, and treatment for 24 weeks combined with ribavirin for positive results.

In the open-label phase 2 LONESTAR study, 40 patients for whom triple therapy comprising a first-generation protease inhibitor had failed (including 55% cirrhotic patients and 85% of patients infected with genotype 1a) were randomised (1:1), with stratification by genotype and the presence or absence of cirrhosis, to 2 groups treated with sofosbuvir + ledipasvir for 12 weeks without ribavirin or with ribavirin (48). SVR was 95% and 100%, respectively, without the presence of cirrhosis or viral sub-type playing a predictive role.

In the phase 3 ION-2 study, 440 patients (including 20% cirrhotic patients, 79% of patients infected with genotype 1a and 52% of patients having experienced failure of treatment comprising telaprevir or boceprevir) were randomised to 4 groups treated for 12 weeks with sofosbuvir + ledipasvir, 12 weeks with sofosbuvir + ledipasvir and ribavirin, 24 weeks with sofosbuvir + ledipasvir and 24 weeks with sofosbuvir + ledipasvir and ribavirin (64). SVR was 92%, 96%, 99% and 99%, respectively, in the 4 groups. Overall SVR (97%) was not influenced by the type of previous treatment. Among cirrhotic patients, SVR was significantly higher in patients treated for 24 weeks (95% and 100%, respectively,
Genotype 1, previously treated, option 4

Patients infected with HCV genotype 1 for whom treatment with pegylated interferon + ribavirin has failed may be treated with paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 to 24 weeks.

Comments

In the phase 3 SAPPHIRE study, 394 non-cirrhotic patients for whom treatment with pegylated interferon + ribavirin had failed were randomised to 2 groups and treated with paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks or placebo for 12 weeks followed by this combination for 12 weeks (53). SVR was 96% (95% in null responders, 100% in partial responders and 95% in relapsers), without any influence arising from sub-type, or type of treatment failure.

In the TURQUOISE II (phase 3) study, 220 cirrhotic patients (141 infected with genotype 1a and 74 with 1b) for whom combined pegylated interferon + ribavirin had failed were randomised and treated with this same combination with the addition of ribavirin for 12 or 24 weeks (55). SVR was comparable in the 2 groups, 92% and 96%, respectively. According to the multivariate analysis, the fact of being a null responder and being infected with genotype 1a were predictive factors for treatment failure. Among cirrhotic patients who were null responders and infected with genotype 1a, SVR was 80% when the patients were treated for 12 weeks versus 93% when the patients were treated for 24 weeks. However, due to the limited sample size, treatment for 24 weeks is recommended in cirrhotic patients with genotype 1a, regardless of the type of treatment failure with pegylated interferon + ribavirin.

In the PEARL II (phase 2) study, 179 non-cirrhotic patients infected with genotype 1b, for whom treatment with pegylated interferon + ribavirin had failed, were randomised and treated with the same
combination without or with ribavirin for 12 weeks (67). SVR rates were comparable in the 2 groups, 97% and 100%, respectively, suggesting that this combination for 12 weeks without ribavirin could be sufficient in these patients.

In the GIFT-I study, 363 Japanese patients infected with genotype 1b were treated with paritaprevir/ritonavir + ombitasvir for 12 weeks (35% of patients having experienced treatment failure among the 321 non-cirrhotic patients and 79% of cirrhotic patients). SVR was 97% in non-cirrhotic patients and 90% in cirrhotic patients (56).

**Genotype 1, previously treated, option 5**

Patients infected with HCV genotype 1 for whom treatment with pegylated interferon + ribavirin ± first-generation protease inhibitor has failed may be treated with grazoprevir + elbasvir ± ribavirin for 12 weeks.

**Comments**

In the C-WORTHY phase 2 study, 130 null responders (including 37% cirrhotic patients) were randomised to 4 arms and treated with this combination with or without ribavirin for 12 to 18 weeks (57). Overall SVR was 95% among null responders, without any influence arising from the presence or absence of ribavirin, sub-type 1a or 1b or the presence or absence of cirrhosis.

In the C-SALVAGE study, 79 patients already treated with boceprevir, telaprevir, or simeprevir (83% of patients having experienced treatment failure and 17% of patients having discontinued treatment prematurely due to poor tolerability) were treated with grazoprevir + elbasvir + ribavirin for 12 weeks. SVR was 96% in the overall population, 95% in the event of treatment failure and 100% in the event of poor tolerability to the previous treatment, 91% after having received boceprevir, 90% after having received telaprevir and 100% after having received simeprevir (68).

**Genotype 1, previously treated, option 6**

Patients infected with HCV genotype 1b for whom treatment with pegylated interferon + ribavirin has failed may be treated with the combination asunaprevir + daclatasvir + beclabuvir for 12 weeks.

**Comments**

In the open-label, phase 3 UNITY-1 study, 103 patients for whom treatment with pegylated interferon + ribavirin had failed were treated with daclatasvir + asunaprevir + beclabuvir for 12 weeks, with SVR
rates of 89% (85% in patients infected with genotype 1a and 100% in patients infected with genotype 1b) (61).

In the UNITY-2 (phase 3) study, 90 cirrhotic patients, for whom treatment with pegylated interferon + ribavirin had failed, were randomised to 2 groups treated with this combination in addition to ribavirin or placebo. SVR was 87% and 93%, respectively (62).

**Genotype 1, previously treated, option 7**

Patients infected with HCV genotype 1 for whom treatment with pegylated interferon + ribavirin ± first-generation protease inhibitor has failed may be treated with sofosbuvir + GS-5816 for 12 weeks.

**Comments**

In the study conducted by Pianko et al., 108 patients with genotype 1, for whom treatment comprising a first-generation protease inhibitor had failed, were randomised to 4 groups and treated with sofosbuvir + GS-5816 (25 or 100 mg/day) with or without ribavirin for 12 weeks (69). SVR ranged from 96% to 100% according to the groups.
1. The following therapeutic options are recommended for genotype 1 non-cirrhotic, treatment-experienced patients:
   - Sofosbuvir + simeprevir for 12 weeks in patients infected with genotype 1b for whom treatment with pegylated interferon + ribavirin has failed (B)
   - Sofosbuvir + daclatasvir for 12 weeks (A)
   - Sofosbuvir + ledipasvir for 12 weeks (A)
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks in patients infected with genotype 1a for whom treatment with pegylated interferon + ribavirin has failed (A).
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir for 12 weeks in patients infected with genotype 1b for whom treatment with pegylated interferon + ribavirin has failed (A).

2. The following therapeutic options may be recommended for genotype 1 non-cirrhotic, treatment-experienced patients:
   - Grazoprevir + elbasvir for 12 weeks (A)
   - Asunaprevir + daclatasvir + beclabuvir for 12 weeks in patients infected with genotype 1b for whom treatment with pegylated interferon + ribavirin has failed (C)
   - Sofosbuvir + GS-5816 for 12 weeks (B)

3. The following therapeutic options are recommended for treatment-experienced genotype 1 patients with compensated cirrhosis:
   - Sofosbuvir + daclatasvir + ribavirin for 12 weeks (C)
   - Sofosbuvir + daclatasvir for 24 weeks (A)
   - Sofosbuvir + ledipasvir + ribavirin for 12 weeks (A)
   - Sofosbuvir + ledipasvir for 24 weeks (A)
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 24 weeks in patients with genotype 1a for whom treatment with pegylated interferon + ribavirin has failed (A)
   - Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks in patients with genotype 1b for whom treatment with pegylated interferon + ribavirin has failed (A)

4. The following therapeutic option may be recommended for treatment-experienced genotype 1 patients with compensated cirrhosis:
   - Grazoprevir + elbasvir + ribavirin for 16 weeks (C)
7.2. Treatment of genotype 2 patients

Two options are available for the treatment of patients infected with genotype 2. These two options do not contain interferon:

- Sofosbuvir + ribavirin for 12 to 16 weeks
- Sofosbuvir + daclatasvir ± ribavirin for 24 weeks

Another option containing pegylated interferon is indicated for second-line treatment:

- Sofosbuvir + ribavirin + pegylated interferon for 12 weeks

The choice of strategy depends on the presence or absence of cirrhosis and previous treatments. The results of the main studies are shown in Table 7.

**Genotype 2, option 1**

Patients infected with HCV genotype 2 may be treated with sofosbuvir + ribavirin for 12 or 16 weeks.

**Comments**

Four phase 3 studies have evaluated the combination sofosbuvir + ribavirin. In the FISSION study, among treatment-naive patients treated for 12 weeks, SVR was 95% (69/73) (70). SVR was superior among non-cirrhotic patients relative to patients with cirrhosis (97% versus 83%). In the POSITRON study which included patients who were ineligible or intolerant to treatment with interferon, the SVR rate obtained with this combination for 12 weeks was 93% (101/109) (71). Comparing the treatment duration of 12 weeks and 16 weeks in the FUSION study, SVR was 86% (31/36) versus 94% (30/32), and 60% (6/10) versus 78% (7/9), respectively, among cirrhotic patients. Hence, patients with cirrhosis could derive benefit from treatment for more than 12 weeks. In the VALENCE trial (72), SVR after 12 weeks of treatment was 93% (68/73). SVR was 94% (59/63) among non-cirrhotic patients and 82% among patients with cirrhosis. Lastly, SVR was 97% (29/30), 100% (2/2), 94% (30/32) and 78% (7/9) among non-cirrhotic treatment-naive patients, cirrhotic treatment-naive patients, non-cirrhotic treatment-experienced patients and cirrhotic treatment-experienced patients, respectively. The combination sofosbuvir + ribavirin was well tolerated. No virologic breakthrough was observed among compliant patients and relapses were not associated with the selection of resistance-associated variants.

In an open-label, phase 3 study conducted in Japan, 90 treatment-naive patients and 63 treatment-experienced patients infected with genotype 2 were treated with sofosbuvir + ribavirin for 12 weeks (73). 60% of these patients corresponded to genotype 2a. Among the 90 treatment-naive patients, SVR
was 98%. Among the 63 treatment-experienced patients, SVR was 95%. The SVR rate was 94% in cirrhotic patients. There were no treatment discontinuations related to adverse reactions.

In TARGET, genotype 2 patients were treated with sofosbuvir + ribavirin for 12 weeks. After 4 weeks of treatment, SVR was 90% (168/187), 91% among non-cirrhotic patients (116/128) and 88% among cirrhotic patients (52/59) (43). This therapeutic regimen was evaluated in 148 treatment-naive Asian patients (7% cirrhotic patients) and 68 treatment-experienced Asian patients (24% cirrhotic patients). SVR was 97% and 100% among treatment-naive and treatment-experienced patients, respectively (74).

**Genotype 2, option 2**

Patients infected with HCV genotype 2 may be treated with sofosbuvir + daclatasvir with or without ribavirin for 24 weeks.

**Comments**

In an open-label study, 26 treatment-naive patients infected with genotype 2 were treated with sofosbuvir + daclatasvir ± ribavirin for 24 weeks (46). SVR was 92% (24/26). Given the potential efficacy of this combination, it may be proposed for more difficult patients, for example, those having experienced treatment failure with pegylated interferon + ribavirin, presenting decompensated cirrhosis.

**Genotype 2, option 3**

Patients infected with HCV genotype 2 may be treated with sofosbuvir + pegylated interferon + ribavirin for 12 weeks.

**Comments**

In a non-controlled phase 2 study (LONESTAR 2), 23 treatment-experienced patients, including 14 cirrhotic patients (2 non-responders and 21 relapsers or patients presenting breakthrough) infected with genotype 2 were treated with sofosbuvir + pegylated interferon + ribavirin for 12 weeks (75). SVR was 96% (22/23).

In a randomised study (BOSON study) on 48 cirrhotic patients experiencing treatment failure with pegylated interferon + ribavirin, SVR was 94% (15/16) after treatment with pegylated interferon +
ribavirin + sofosbuvir for 12 weeks, 100% (17/17) after treatment with sofosbuvir + ribavirin for 24 weeks and 87% (13/15) after treatment with sofosbuvir + ribavirin for 16 weeks (76).

RECOMMENDATIONS

1. Treatment with sofosbuvir + ribavirin for 12 weeks is recommended for treatment-naive genotype 2 patients (A)

2. The following therapeutic options are recommended in non-cirrhotic genotype 2 patients for whom treatment with pegylated interferon + ribavirin has failed:
   - Sofosbuvir + ribavirin for 12 weeks (C)
   - Sofosbuvir + daclatasvir for 12 weeks (EA)

3. The following therapeutic options are recommended in genotype 2 patients with compensated cirrhosis for whom treatment with pegylated interferon + ribavirin has failed:
   - Sofosbuvir + ribavirin for 24 weeks (C)
   - Sofosbuvir + daclatasvir for 12 weeks (EA)

7.3. Treatment of genotype 3 patients

There are numerous corroborating arguments which show that genotype 3 is associated with a higher risk of cirrhosis and hepatocellular carcinoma compared with the other genotypes (4). Moreover, as treatment efficacy is lower among genotype 3 cirrhotic patients, therapeutic regimens with SVR < 90% may be recommended. Three options are available for the treatment of patients infected with genotype 3. These three options do not contain interferon:
   - Sofosbuvir + ribavirin for 12, 16, or 24 weeks
   - Sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks
   - Sofosbuvir + ledipasvir + ribavirin for 12 weeks.

Another option containing interferon is available:
   - Sofosbuvir + ribavirin + pegylated interferon for 12 weeks

Another combination is currently in development:
   - Sofosbuvir + GS-5816 for 12 weeks.

The choice of strategy depends on the presence or absence of cirrhosis and previous treatments. The results of the main studies are shown in Table 8.
**Genotype 3, option 1**

Patients infected with HCV genotype 3 may be treated with sofosbuvir + ribavirin for 24 weeks.

**Comments**

This combination is rather intended for patients with mild or moderate fibrosis. The results of the phase 3 studies are all along the same lines. In the FISION (70) and POSITRON (71) studies, this combination for 12 weeks yielded disappointing results, with SVR rates of 56% and 61%, respectively. In the FISION study, the results were even more disappointing among cirrhotic patients (SVR 34%). In the FUSION study (71), when increasing the treatment duration to 16 weeks, SVR was still only 62%. In the VALENCE study, which proposed a treatment duration of 24 weeks, SVR rate was 94% in non-cirrhotic treatment-naive patients, 92% in cirrhotic treatment-naive patients, 87% in non-cirrhotic treatment-experienced patients, and 60% in cirrhotic treatment-experienced patients (77).

**Genotype 3, option 2**

Patients infected with HCV genotype 3 may be treated with sofosbuvir + daclatasvir ± ribavirin for 12 to 24 weeks.

**Comments**

The first study to have been published was a phase 2B study (46). With this strategy proposed to 18 non-cirrhotic treatment-naive patients, SVR was 89%, without any impact arising from ribavirin. In the ALLY-3 study, 152 patients were treated with sofosbuvir + daclatasvir, without ribavirin, for 12 weeks. SVR rate was 97% in non-cirrhotic treatment-naive patients, 58% in cirrhotic treatment-naive patients, 94% in non-cirrhotic treatment-experienced patients and 69% in cirrhotic treatment-experienced patients (20).

In the preliminary study of data relating to the Temporary Authorisation for Use (ATU) for daclatasvir, 88 cirrhotic patients were treated with sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks. SVR4 was 76% for the 29 patients treated for 12 weeks and 88% for the 59 patients treated for 24 weeks (78).
**Genotype 3, option 3**
Patients infected with HCV genotype 3 may be treated with sofosbuvir + ledipasvir + ribavirin for 12 to 24 weeks.

**Comments**
No studies have yet been published. The preliminary results of the ELECTRON-2 study concerned 51 treatment-naive patients, including 8 patients with cirrhosis (79). All patients were treated for 12 weeks, 25 patients without ribavirin and 26 patients with ribavirin. SVR was 64% and 100%, respectively.

Another study evaluated 50 patients having already received previous treatment and having been treated with sofosbuvir + ledipasvir + ribavirin for 12 weeks (80). SVR was 89% in non-cirrhotic patients, and 73% in cirrhotic patients. Ledipasvir does not display an optimum in vitro antiviral activity on genotype 3. Under these conditions, this option is not recommended.

**Genotype 3, option 4**
Patients infected with HCV genotype 3 may be treated with pegylated interferon + ribavirin + sofosbuvir for 12 weeks.

**Comments**
In the LONESTAR-2 study, 12 patients fulfilling these criteria were treated with this combination (75). SVR was 83%, identical to that observed among non-cirrhotic patients. This result should be compared with those obtained in the VALENCE study. Among 45 patients fulfilling these criteria, SVR was only 60% among patients treated with sofosbuvir + ribavirin without interferon for 24 weeks (72). Obviously the "CUPIC" criteria should be taken into account if this strategy with interferon is chosen as this concerns cirrhotic patients: platelet count > 100,000/mm3 and albumin > 35 g/L.

In a study on 544 patients, 181 patients (38% cirrhotic patients and 52% patients having experienced treatment failure with pegylated interferon + ribavirin) were treated with pegylated interferon + ribavirin + sofosbuvir. SVR was 93%, compared with 71% and 84% in patients treated with sofosbuvir + ribavirin for 16 weeks (181 patients, including 37% cirrhotic patients) and 24 weeks (182 patients including 37% cirrhotic patients), respectively (76).
Genotype 3, option 5
Patients infected with HCV genotype 3 may be treated with sofosbuvir + GS-5816 for 12 weeks.

Comments
The initial results obtained for the combination sofosbuvir + GS-5816 seem very promising. Among the 210 patients having already received treatment, and treated with the combination sofosbuvir + GS-5816 ± ribavirin for 12 weeks, SVR was 95% in non-cirrhotic patients, and 81% in cirrhotic patients (90% with ribavirin) (35).

RECOMMENDATIONS

1. The following therapeutic option is recommended for genotype 3 non-cirrhotic patients:
   - Sofosbuvir + daclatasvir for 12 weeks (A)

2. The following therapeutic options are recommended for genotype 3 patients with compensated cirrhosis:
   - Sofosbuvir + pegylated interferon + ribavirin for 12 weeks (B)
   - Sofosbuvir + daclatasvir + ribavirin for 24 weeks (B)

3. The following therapeutic option may be recommended for genotype 3 non-cirrhotic patients:
   - Sofosbuvir + GS-5816 for 12 weeks (B)

4. The following therapeutic option may be recommended for genotype 3 patients with compensated cirrhosis:
   - Sofosbuvir + GS-5816 + ribavirin for 12 weeks (B)

RECOMMENDATIONS

1. Treatment with sofosbuvir + ledipasvir is not recommended for genotype 3 patients (A)
7.4. Treatment of genotype 4 patients

Limited therapeutic studies have been performed in genotype 4 patients, and usually involve pilot studies with limited sample sizes. Five options without interferon are available for the treatment of patients infected with genotype 4:

- Sofosbuvir + ribavirin for 24 weeks
- Sofosbuvir + simeprevir for 12 weeks
- Sofosbuvir + daclatasvir for 12 weeks
- Sofosbuvir + ledipasvir for 12 weeks
- Paritaprevir/ritonavir + ombitasvir + ribavirin for 12 weeks

Three other combinations are currently in development:

- Grazoprevir + elbasvir for 12 weeks
- Asunaprevir + daclatasvir + beclabuvir for 12 weeks
- Sofosbuvir + GS-5816 ± ribavirin for 12 weeks

The choice of strategy depends on the presence or absence of cirrhosis and previous treatments. The results of the main studies are shown in Table 9.

**Genotype 4, option 1**

Patients infected with HCV genotype 4 may be treated with sofosbuvir + ribavirin for 24 weeks.

**Comments**

The combination sofosbuvir + ribavirin for 24 weeks (60 patients of Egyptian origin, including 23% cirrhotic patients) yielded SVR rates between 100% (treatment-naive patients) and 87% (treatment-experienced patients) (81). These results were confirmed in a second study on 103 Egyptian patients treated for 24 weeks, with SVR rates of 92% in treatment-naive patients and 89% in treatment-experience patients (82). The presence of cirrhosis was the reason for the reduction in SVR (93% versus 78%). Option 1 is not recommended for SVR < 90%.
**Genotype 4, option 2**

Patients infected with HCV genotype 4 may be treated with sofosbuvir + simeprevir ± ribavirin for 12 weeks.

**Comments**
In the HEPATHER cohort, the combination sofosbuvir + simeprevir for 12 to 24 weeks was evaluated in 34 patients (7 patients received ribavirin in addition) (83). Irrespective of the therapeutic regimen, SVR4 was 100% regardless of the presence or absence of cirrhosis when the patients received treatment with ribavirin.

**Genotype 4, option 3**

Patients infected with HCV genotype 4 may be treated with sofosbuvir + daclatasvir for 12 weeks.

**Comments**
In the HEPATHER cohort, the combination sofosbuvir + daclatasvir ± ribavirin for 12 to 24 weeks was evaluated in 48 patients (15 patients received ribavirin in addition) (83). Irrespective of the therapeutic regimen, SVR4 was 100% regardless of the presence or absence of cirrhosis when the patients received treatment with ribavirin.

**Genotype 4, option 4**

Patients infected with HCV genotype 4 may be treated with sofosbuvir + ledipasvir for 12 weeks.

**Comments**
The combination sofosbuvir + ledipasvir for 12 weeks in 21 treatment-naive or treatment-experienced patients (38%), with (33%) or without cirrhosis yielded a 95% SVR (84). In a recent French study on 44 patients (23% cirrhotic patients), SVR was 93% (85). In the absence of data, by analogy with genotype 1, addition of ribavirin is recommended in patients with compensated cirrhosis.
**Genotype 4, option 5**
Patients infected with HCV genotype 4 may be treated with paritaprevir/ritonavir + ombitasvir + ribavirin for 12 weeks.

**Comments**
The combination paritaprevir/ritonavir + ombitasvir + ribavirin (135 non-cirrhotic patients) for 12 weeks yielded SVR rates of 91% in treatment-naive patients receiving treatment not including ribavirin and 100% in treatment-naive and treatment-experienced patients with ribavirin (86). Resistance-associated variants with NS3 and NS5A mutations were identified in the 3 treatment-naive patients without ribavirin experiencing virologic failure.

**Genotype 4, option 6**
Patients infected with HCV genotype 4 may be treated with grazoprevir + elbasvir for 12 weeks.

**Comments**
Among 26 treatment-naive patients, the combination grazoprevir + elbasvir for 12 weeks yielded a 100% SVR, irrespective of fibrosis stage (59).

**Genotype 4, option 7**
Patients infected with HCV genotype 4 may be treated with daclatasvir + asunaprevir + beclabuvir for 12 weeks.

**Comments**
Among 21 treatment-naive and non-cirrhotic patients, the combination asunaprevir + daclatasvir + beclabuvir for 12 weeks yielded a 100% SVR irrespective of beclabuvir dosage strength (75 and 150 mg) (87).
Genotype 4, option 8

Patients infected with HCV genotype 4 may be treated with sofosbuvir + GS-5816 for 12 weeks.

Comments

The combination sofosbuvir + GS-5816 for 12 weeks yielded SVR rates of 86% (GS-5816 containing 25 mg) and 100% (GS-5816 containing 100 mg) in 14 treatment-naive and non-cirrhotic patients (63).

RECOMMENDATIONS

1. The following therapeutic options are recommended for genotype 4 non-cirrhotic patients:
   - Sofosbuvir + simeprevir for 12 weeks (C)
   - Sofosbuvir + daclatasvir for 12 weeks (C)
   - Sofosbuvir + ledipasvir for 12 weeks (B)
   - Paritaprevir/ritonavir + ombitasvir + ribavirin for 12 weeks (A)

2. The following therapeutic options are recommended for genotype 4 patients with compensated cirrhosis:
   - Sofosbuvir + simeprevir + ribavirin for 12 weeks (C)
   - Sofosbuvir + simeprevir for 24 weeks (C)
   - Sofosbuvir + daclatasvir + ribavirin for 12 weeks (C)
   - Sofosbuvir + daclatasvir for 24 weeks (C)
   - Sofosbuvir + ledipasvir + ribavirin for 12 weeks (EA)

3. The following therapeutic options may be recommended for genotype 4 non-cirrhotic, treatment-naive patients:
   - Grazoprevir + elbasvir for 12 weeks (C)
   - Sofosbuvir + GS-5816 for 12 weeks (C)
7.5. Treatment of genotype 5 or 6 patients

Two therapeutic options without interferon are available:

- Sofosbuvir + daclatasvir for 12 weeks
- Sofosbuvir + ledipasvir for 12 weeks

Another combination is currently in development:

- Grazoprevir + elbasvir for 12 weeks

The choice of strategy depends on the presence or absence of cirrhosis and previous treatments. The results of the main studies are shown in Table 10.

**Genotype 5 or 6, option 1**

Patients infected with HCV genotype 5 or 6 may be treated with sofosbuvir + daclatasvir for 12 weeks.

**Comments**

Daclatasvir displays *in vitro* antiviral activity against genotypes 5 and 6. No data are available *in vivo* on efficacy and safety in combination with sofosbuvir. In the absence of data, by analogy with genotype 1, addition of ribavirin is recommended in patients with compensated cirrhosis.

**Genotype 5 or 6, option 2**

Patients infected with HCV genotype 5 or 6 may be treated with sofosbuvir + ledipasvir for 12 weeks.

**Comments**

Ledipasvir displays *in vitro* antiviral activity against genotypes 5 and 6. Among genotype 5 patients, the combination sofosbuvir + ledipasvir without ribavirin for 12 weeks was evaluated in 41 patients. SVR was 95% (39/41), 95% in treatment-naive patients (20/21) and treatment-experienced patients (19/20), 97% (31/32) in non-cirrhotic patients and 89% (8/9) in cirrhotic patients. The two cases of failure were related to relapse (85).

This combination was administered without ribavirin for 12 weeks in 25 treatment-naive or treatment-experienced patients, infected with genotype 6. SVR was 96% (24/25) (80). No data are available for cirrhotic patients. In the absence of data, by analogy with genotype 1, addition of ribavirin is recommended in patients with compensated cirrhosis.
Genotype 5 or 6, option 3

Grazoprevir and elbasvir display antiviral activity against genotypes 5 and 6. However, the combination grazoprevir + elbasvir is not recommended in patients infected with genotype 5 or 6.

Comments
The combination grazoprevir + elbasvir was evaluated without ribavirin for 12 weeks in 8 non-cirrhotic treatment-naive patients, infected with genotype 5. SVR was only observed in 5 out of 8 patients (88). Failure was observed in 3 patients who had not received ribavirin and was related to virologic breakthrough in one case and relapse in the other two cases.

Twenty-four patients infected with genotype 6, treatment-naive or treatment-experienced, without any information being provided on fibrosis stage, were included in three trials. They received the combination grazoprevir + elbasvir with or without ribavirin for 12 to 16 weeks. SVR was 79% (19/24) (89). SVR was 78% (14/18) in patients who did not receive ribavirin and 83% (5/6) in patients treated with ribavirin. Relapse was observed in 3 patients and virological breakthrough in one patient. In one case, the cause of failure was not determined.

Due to the overall low SVR rates and the existence of virological breakthrough, this strategy comprising grazoprevir + elbasvir cannot be recommended for patients infected with genotype 5 or 6.

RECOMMENDATIONS

1. The following therapeutic options are recommended for genotype 5 or 6 non-cirrhotic patients:
   - Sofosbuvir + daclatasvir for 12 weeks (EA)
   - Sofosbuvir + ledipasvir for 12 weeks (B)
2. The following therapeutic options are recommended for genotype 5 or 6 patients with compensated cirrhosis:
   - Sofosbuvir + daclatasvir + ribavirin for 12 weeks (EA)
   - Sofosbuvir + daclatasvir for 24 weeks (EA)
   - Sofosbuvir + ledipasvir + ribavirin for 12 weeks (C)
   - Sofosbuvir + ledipasvir for 24 weeks (C)
Table 5. Treatment outcomes for genotype 1 treatment-naive patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Genotype</th>
<th>N</th>
<th>Cirrhosis (%)</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lait E et al</td>
<td>PR + SOF 12 wk</td>
<td>1</td>
<td>291</td>
<td>17</td>
<td>89</td>
<td>(70)</td>
</tr>
<tr>
<td>Dieterich D et al.</td>
<td>TRIO PR + SOF 12 wk</td>
<td>1</td>
<td>169</td>
<td>NA</td>
<td>81</td>
<td>(42)</td>
</tr>
<tr>
<td>Jenssen et al</td>
<td>PR SOF 12 wk</td>
<td>1</td>
<td>127</td>
<td>100</td>
<td>70</td>
<td>(43)</td>
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<tr>
<td>Osinusi A et al</td>
<td>SOF RBV 24 wk</td>
<td>1</td>
<td>10</td>
<td>No</td>
<td>90</td>
<td>(39)</td>
</tr>
<tr>
<td>Osinusi A et al</td>
<td>SOF RBV 24 wk</td>
<td>1</td>
<td>50</td>
<td>26% F3F4</td>
<td>68</td>
<td>(39)</td>
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<tr>
<td>Gane EJ et al</td>
<td>SOF RBV 24 wk</td>
<td>1</td>
<td>25</td>
<td>No</td>
<td>84</td>
<td>(40)</td>
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<tr>
<td>Lawitz E et al</td>
<td>COSMOS SOF SIM ± 12 – 24 wk</td>
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<td>39</td>
<td>F3F4</td>
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<td>(41)</td>
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<tr>
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<td>TRIO SOF SIM ± RBV 12 wk</td>
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<td>92</td>
<td>84</td>
<td>(90)</td>
</tr>
<tr>
<td>Jenssen D et al</td>
<td>TARGET SOF SIM 12 wk</td>
<td>1</td>
<td>378</td>
<td>NA</td>
<td>87</td>
<td>(43)</td>
</tr>
<tr>
<td>Jenssen D et al</td>
<td>TARGET SOF SIM RBV 12 wk</td>
<td>1</td>
<td>378</td>
<td>NA</td>
<td>89</td>
<td>(43)</td>
</tr>
<tr>
<td>Kwo P et al</td>
<td>OPTIMIST-1 SOF SIM 12 wk</td>
<td>1</td>
<td>218</td>
<td>No</td>
<td>97</td>
<td>85</td>
</tr>
<tr>
<td>Lawitz E et al</td>
<td>OPTIMIST-2 SOF SIM 12 wk</td>
<td>1</td>
<td>103</td>
<td>100</td>
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<tr>
<td>Sulkowski M et al</td>
<td>SOF DCV ± RBV 12 or 24 wk</td>
<td>1</td>
<td>126</td>
<td>13</td>
<td>99-100</td>
<td>(91)</td>
</tr>
<tr>
<td>POL S et al</td>
<td>HEPATHER SOF DCV ± RBV 12 - 24 wk</td>
<td>1</td>
<td>409</td>
<td>78</td>
<td>Cirrhosis 100</td>
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<tr>
<td></td>
<td>SOF DCV 12 wk</td>
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<td></td>
<td></td>
<td></td>
<td>(47)</td>
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<tr>
<td></td>
<td>SOF DCV RBV 12 wk</td>
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<td></td>
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<td>SOF DCV 24 wk</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lawitz E et al</td>
<td>ION-1 SOF LDV 12 wk</td>
<td>1</td>
<td>19</td>
<td>No</td>
<td>95</td>
<td>(48)</td>
</tr>
<tr>
<td>Afadhil N et al</td>
<td>ION-1 SOF LDV 12 wk</td>
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<td>214</td>
<td>16%</td>
<td>99</td>
<td>(49)</td>
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<tr>
<td>Kowdley KV et al</td>
<td>ION-3 SOF LDV 12 wk</td>
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<td>216</td>
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<td>95</td>
<td>(50)</td>
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<td>Study</td>
<td>Treatment</td>
<td>Duration</td>
<td>Week 1</td>
<td>Week 12</td>
<td>SVR12</td>
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<td>---------</td>
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<td>Reddy KR et al</td>
<td>SOF LDV RBV 12 wk</td>
<td>1</td>
<td>161</td>
<td>100</td>
<td>96</td>
<td>(51)</td>
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<td>Buggisch P et al.</td>
<td>SOF LDV 8 wk</td>
<td>1</td>
<td>45</td>
<td>0</td>
<td>100</td>
<td>(52)</td>
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<tr>
<td>Feld JJ et al, SAPPHIRE-1</td>
<td>3D RBV 12 wk</td>
<td>1</td>
<td>473</td>
<td>No</td>
<td>96</td>
<td>(53)</td>
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<tr>
<td>Ferenci P et al, PEARL-III</td>
<td>3D ± RBV 12 wk</td>
<td>1b</td>
<td>419</td>
<td>No</td>
<td>99</td>
<td>(5)</td>
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<tr>
<td>Ferenci P et al, PEARL-IV</td>
<td>3D RBV 12 wk</td>
<td>1a</td>
<td>305</td>
<td>No</td>
<td>97</td>
<td>(54)</td>
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<tr>
<td>Fried MW et al, TURQUOISE-II</td>
<td>3D RBV 12 wk</td>
<td>1</td>
<td>380</td>
<td>100</td>
<td>92</td>
<td>(92)</td>
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<tr>
<td>Chayama K et al, GIFT-1</td>
<td>2D 12 wk</td>
<td>1b</td>
<td>363</td>
<td>Yes</td>
<td>96</td>
<td>(56)</td>
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<tr>
<td>Poordad F et al, UNITY-1</td>
<td>DCV (30 mg/day) ASV BCV 12 wk</td>
<td>1</td>
<td>312</td>
<td>No</td>
<td>92</td>
<td>(61)</td>
</tr>
<tr>
<td>Muir A et al, UNITY-2</td>
<td>DCV (30 mg/day) ASV BCV RBV 12 wk</td>
<td>1</td>
<td>112</td>
<td>100</td>
<td>98</td>
<td>(93)</td>
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<td>Zeuzem S et al, C-EDGE</td>
<td>GZR EBR 12 wk</td>
<td>1</td>
<td>210</td>
<td>22</td>
<td>95</td>
<td>(59)</td>
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<tr>
<td>Poordad F et al, C-SWIFT</td>
<td>GZR EBR 4 – 8 wk</td>
<td>1</td>
<td>102</td>
<td>0</td>
<td>33 – 87</td>
<td>(60)</td>
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<td>GZR EBR 6 – 8 wk</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>80 - 94</td>
<td>(60)</td>
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<td>Tran T et al</td>
<td>SOF + GS-5816 25 or 100 mg/day 12 wk</td>
<td>1</td>
<td>55</td>
<td>0</td>
<td>96 - 100</td>
<td>(63)</td>
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NA: not available; TF: previous treatment failure with pegylated interferon + ribavirin; PR: pegylated interferon + ribavirin; SOF: sofosbuvir; wk: weeks; DCV: daclatasvir; SIM: simeprevir; RBV: ribavirin; LDV: ledipasvir; ASV: asunaprevir; 3D: paritaprevir/ritonavir + ombitasvir + dasabuvir; 2D: paritaprevir/ritonavir + ombitasvir; BCV: beclabuvir; GZR: grazoprevir; EBR: Elbasvir
Table 6. Treatment outcomes for genotype 1 patients for whom treatment with pegylated interferon + ribavirin has failed (with or without telaprevir or boceprevir)

<table>
<thead>
<tr>
<th>Author</th>
<th>Indication</th>
<th>Genotype</th>
<th>N</th>
<th>Cirrhosis (%)</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gane EJ et al</td>
<td>SOF RBV 12 wk</td>
<td>1</td>
<td>10</td>
<td>no</td>
<td>10</td>
<td>(40)</td>
</tr>
<tr>
<td>Lawitz E et al</td>
<td>Cohort 1</td>
<td>1</td>
<td>80</td>
<td>24</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>SOF SMV RBV 24 wk</td>
<td></td>
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<td>15</td>
<td>0</td>
<td>93</td>
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<tr>
<td></td>
<td>SOF SMV 24 wk</td>
<td></td>
<td></td>
<td>27</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>SOF SMV RBV 12 wk</td>
<td></td>
<td></td>
<td>14</td>
<td>0</td>
<td>93</td>
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<tr>
<td>Dieterich D et al. TRIO</td>
<td>PR SOF 12 wk</td>
<td>1</td>
<td>76</td>
<td>NA</td>
<td>70</td>
<td>(42)</td>
</tr>
<tr>
<td>Dieterich D et al. TRIO</td>
<td>SOF SMV ± RBV 12 wk</td>
<td>1</td>
<td>166</td>
<td>45</td>
<td>83</td>
<td>(90)</td>
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<td>Reddy KR et al. ATTAIN</td>
<td>PR SMV 24 wk</td>
<td>1</td>
<td>379</td>
<td>23</td>
<td>54</td>
<td>(94)</td>
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<tr>
<td>Kwo P et al. OPTIMIST-1</td>
<td>SOF SIM 8-12 wk</td>
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<td>0</td>
<td>97-83</td>
<td>(44)</td>
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<tr>
<td>Lawitz E et al. OPTIMIST-2</td>
<td>SOF SIM 12 wk</td>
<td>1</td>
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<td>100</td>
<td>79</td>
<td>(45)</td>
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<td>SOF SIM 12 wk</td>
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<td>NA</td>
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<td>85</td>
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<td>SOF SIM RBV 12 wk</td>
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<tr>
<td>Pol S et al. HEPATHER</td>
<td>SOF DCV ± RBV 12-24 wk</td>
<td>1</td>
<td>306</td>
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<td>100 if</td>
<td>(47)</td>
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<td>not F4</td>
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<tr>
<td>Lawitz E et al.</td>
<td>SOF LDV 12 wk</td>
<td>1</td>
<td>19</td>
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<td>100</td>
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<td>Afdhal N et al</td>
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<td>SOF LDV RBV 12 wk</td>
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<td>SOF LDV 24 wk</td>
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<td>SOF LDV RBV 24 wk</td>
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<tr>
<td>Reddy KR et al</td>
<td>SOF LDV +/- RBV 12 wk or 24 wk</td>
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<td>100</td>
<td>95</td>
<td>(51)</td>
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<tr>
<td>Bourlière M et al.</td>
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<td>Treatment</td>
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<td>V2 Data</td>
<td>V3 Data</td>
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<td>SIRIUS</td>
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<tr>
<td>Chayama K et al.</td>
<td>2D RBV 12 wk</td>
<td>1b</td>
<td>145</td>
<td>12</td>
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<td>2D RBV 24 wk</td>
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<tr>
<td>Andreone P et al.</td>
<td>3D 12 wk</td>
<td>1b</td>
<td>179</td>
<td>0</td>
<td>97 (95)</td>
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<td>PEARL II</td>
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<td>Zeuzem S et al.</td>
<td>3D RBV 12 wk</td>
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<td>96 (72)</td>
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<td>3D RBV 12 wk</td>
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<td>Poordad F et al.</td>
<td>3D RBV 12 wk</td>
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<td>220</td>
<td>100</td>
<td>90 (92)</td>
<td></td>
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<td>Turquoise II</td>
<td>3D RBV 24 wk</td>
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<td></td>
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<tr>
<td>Poordad F et al.</td>
<td>DCV ASV BCV 12 wk</td>
<td>1</td>
<td>103</td>
<td>No</td>
<td>89 (61)</td>
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<tr>
<td>UNITY 1</td>
<td>DCV ASV BCV 12 wk</td>
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<td>Muir A et al</td>
<td>DCV ASV BCV 12 wk</td>
<td>1</td>
<td>90</td>
<td>100</td>
<td>87 (62)</td>
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<td>DCV ASV BCV 12 wk</td>
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<td>Lawitz et al. C-WORTHY</td>
<td>GZV ELV RBV 12 wk</td>
<td>1</td>
<td>32</td>
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<td>94 (57)</td>
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<td>100</td>
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<td>GZV ELV 18 wk</td>
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<td>32</td>
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<td>Pianko S et al</td>
<td>SOF GS-5816 ± RBV 12 wk</td>
<td>1</td>
<td>107</td>
<td>43</td>
<td>85 - 100</td>
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</table>

NA: not available; TF: previous treatment failure with pegylated interferon + ribavirin; PR: pegylated interferon + ribavirin; SOF: sofosbuvir; wk: weeks; DCV: daclatasvir; SIM: simeprevir; RBV: ribavirin; LDV: ledipasvir; ASV: asunaprevir; 3D: paritaprevir/ritonavir + ombitasvir + dasabuvir; 2D: paritaprevir/ritonavir + ombitasvir; BCV: beclabuvir; GZV: grazoprevir; ELV: Elbasvir
Table 7. Treatment outcomes for genotype 2 patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Genotype</th>
<th>N</th>
<th>Cirrhosis</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawitz E et al. FISSION</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>73</td>
<td>Yes</td>
<td>95</td>
<td>(70)</td>
</tr>
<tr>
<td>Jacobson IM et al. POSITRON</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>109</td>
<td>Yes</td>
<td>93</td>
<td>(71)</td>
</tr>
<tr>
<td>Jacobson IM et al. FUSION</td>
<td>SOF RBV 16 wk</td>
<td>2</td>
<td>32</td>
<td>Yes</td>
<td>94</td>
<td>(71)</td>
</tr>
<tr>
<td>Zeuzem S et al. VALENCE</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>73</td>
<td>Yes</td>
<td>93</td>
<td>(77)</td>
</tr>
<tr>
<td>Omata M et al.</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>90</td>
<td>Yes</td>
<td>98</td>
<td>(73)</td>
</tr>
<tr>
<td>Kao JH et al.</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>148</td>
<td>Yes</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>TARGET</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>187</td>
<td>Yes</td>
<td>90</td>
<td>(43)</td>
</tr>
<tr>
<td>Sulkowki MS et al.</td>
<td>SOF DCV ± RBV 24 wk</td>
<td>2</td>
<td>26</td>
<td>-</td>
<td>92</td>
<td>(46)</td>
</tr>
<tr>
<td>Lawitz E et al. LONESTAR 2</td>
<td>PR SOF 12 wk</td>
<td>2</td>
<td>23</td>
<td>TF</td>
<td>96</td>
<td>(75)</td>
</tr>
<tr>
<td>Dieterich D et al. TRIO</td>
<td>SOF RBV 12 wk</td>
<td>2</td>
<td>202</td>
<td>25</td>
<td>85</td>
<td>(90)</td>
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<tr>
<td>Foster GR et al. BOSON</td>
<td>SOF RBV 16-24 wk</td>
<td>2</td>
<td>48</td>
<td>100</td>
<td>87</td>
<td>100</td>
</tr>
</tbody>
</table>

SOF: sofosbuvir; RBV: ribavirin; TF: previous treatment failure with pegylated interferon + ribavirin; DCV: Daclatasvir
Table 8. Treatment outcomes for genotype 3 patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Genotype</th>
<th>N</th>
<th>Cirrhosis (%)</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gane E et al</td>
<td>SOF RBV 12 wk</td>
<td>3 treatment-naive</td>
<td>6</td>
<td>No</td>
<td>100</td>
<td>(40)</td>
</tr>
<tr>
<td>Gane E et al</td>
<td>PR SOF 12 wk</td>
<td>3 treatment-naive</td>
<td>29</td>
<td>No</td>
<td>100</td>
<td>(40)</td>
</tr>
<tr>
<td>Lawitz E et al</td>
<td>SOF RBV 12 wk</td>
<td>3 treatment-naive</td>
<td>183</td>
<td>20</td>
<td>56</td>
<td>(70)</td>
</tr>
<tr>
<td>Jacobson I et al</td>
<td>SOF RBV 12 wk</td>
<td>3 treatment-naive</td>
<td>98</td>
<td>15</td>
<td>61</td>
<td>(71)</td>
</tr>
<tr>
<td>Jacobson I et al</td>
<td>SOF RBV 12 wk or 16 wk</td>
<td>3 TF</td>
<td>127</td>
<td>35</td>
<td>30</td>
<td>(71)</td>
</tr>
<tr>
<td>Zeuzem S et al</td>
<td>SOF RBV 24 wk</td>
<td>3 treatment-naive</td>
<td>105</td>
<td>12</td>
<td>95</td>
<td>(77)</td>
</tr>
<tr>
<td>Zeuzem S et al</td>
<td>SOF RBV 24 wk</td>
<td>3 TF</td>
<td>145</td>
<td>32</td>
<td>87 &lt; F4 62 F4</td>
<td>(77)</td>
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<tr>
<td>Gane E et al</td>
<td>SOF LDV 12 wk</td>
<td>3 treatment-naive</td>
<td>25</td>
<td>16</td>
<td>64</td>
<td>(79)</td>
</tr>
<tr>
<td>Gane E et al</td>
<td>SOF LDV RBV 12 wk</td>
<td>3 treatment-naive</td>
<td>26</td>
<td>16</td>
<td>100</td>
<td>(79)</td>
</tr>
<tr>
<td>Sulkowski MS et al</td>
<td>SOF DCV RBV 24 wk</td>
<td>3 treatment-naive</td>
<td>18</td>
<td>NA</td>
<td>89</td>
<td>(7)</td>
</tr>
<tr>
<td>Dore GJ et al</td>
<td>PR DCV 12 wk or 16 wk</td>
<td>3 treatment-naive</td>
<td>53</td>
<td>73</td>
<td>69 66</td>
<td>(96)</td>
</tr>
<tr>
<td>Nelson DR et al</td>
<td>SOF DCV 12 wk</td>
<td>3 treatment-naive</td>
<td>101</td>
<td>19</td>
<td>90</td>
<td>(22)</td>
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<td>Nelson DR et al</td>
<td>SOF DCV 12 wk</td>
<td>3 TF</td>
<td>51</td>
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<td>(22)</td>
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<tr>
<td>Hézode C. et al.</td>
<td>SOF DCV ± RBV 24 wk</td>
<td>3 treatment-naive and TF</td>
<td>59</td>
<td>100</td>
<td>88</td>
<td>(19)</td>
</tr>
<tr>
<td>Lawitz E et al</td>
<td>PR SOF 12 wk</td>
<td>3 TF</td>
<td>24</td>
<td>50</td>
<td>83</td>
<td>(20)</td>
</tr>
<tr>
<td>Gane E et al</td>
<td>SOF LDV RBV 12 wk</td>
<td>3 TF</td>
<td>50</td>
<td>44</td>
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<td>(80)</td>
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<tr>
<td>Foster G et al.</td>
<td>PR SOF 12 wk</td>
<td>3 treatment-naive and TF</td>
<td>181</td>
<td>38</td>
<td>93T</td>
<td>(76)</td>
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<tr>
<td>Esteban R et al</td>
<td>PR SOF 12 wk</td>
<td>3 TF *</td>
<td>28</td>
<td>36</td>
<td>91</td>
<td>(97)</td>
</tr>
<tr>
<td>Esteban R et al</td>
<td>SOF RBV 24 wk</td>
<td>3 TF *</td>
<td>68</td>
<td>31</td>
<td>63</td>
<td>(97)</td>
</tr>
<tr>
<td>Authors</td>
<td>Treatment</td>
<td>Genotype</td>
<td>N</td>
<td>Cirrhosis</td>
<td>SVR (%)</td>
<td>Reference</td>
</tr>
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<tr>
<td>Lawitz E et al.</td>
<td>PR SOF 12 wk</td>
<td>4</td>
<td>28</td>
<td>Yes</td>
<td>96</td>
<td>(70)</td>
</tr>
<tr>
<td>Hézode C et al.</td>
<td>PR DCV 12 wk</td>
<td>4</td>
<td>12*</td>
<td>Yes</td>
<td>100</td>
<td>(98)</td>
</tr>
<tr>
<td>Moreno C et al.</td>
<td>PR SMV 12 wk</td>
<td>4</td>
<td>107</td>
<td>Yes</td>
<td>65</td>
<td>(99)</td>
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<td>Ruane PJ et al.</td>
<td>SOF RBV 24 wk</td>
<td>4</td>
<td>60</td>
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<td>80</td>
<td>(81)</td>
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<tr>
<td>Esmat GE et al.</td>
<td>SOF RBV 24 wk</td>
<td>4</td>
<td>103</td>
<td>Yes</td>
<td>83</td>
<td>(82)</td>
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<tr>
<td>Hézode C et al.</td>
<td>2D RBV 12 wk</td>
<td>4</td>
<td>135</td>
<td>No</td>
<td>97</td>
<td>(86)</td>
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<tr>
<td>Kapoor R et al.</td>
<td>SOF LDV 12 wk</td>
<td>4</td>
<td>21</td>
<td>Yes</td>
<td>95</td>
<td>(84)</td>
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<tr>
<td>Abergel A et al.</td>
<td>SOF LDV 12 wk</td>
<td>4</td>
<td>44</td>
<td>Yes</td>
<td>93</td>
<td>(85)</td>
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<tr>
<td>Zeuzem S et al.</td>
<td>GZR EBR 12 wk</td>
<td>4</td>
<td>26</td>
<td>Yes</td>
<td>100</td>
<td>(59)</td>
</tr>
<tr>
<td>Hassanein T et al.</td>
<td>ASV DCV BCV 12 wk</td>
<td>4</td>
<td>21</td>
<td>No</td>
<td>100</td>
<td>(87)</td>
</tr>
<tr>
<td>Tran T et al.</td>
<td>SOF GS-5816 12 wk</td>
<td>4</td>
<td>14</td>
<td>No</td>
<td>93</td>
<td>(63)</td>
</tr>
</tbody>
</table>

* Including patients having experience treatment failure with sofosbuvir + ribavirin 12 weeks

NA: not available; TF: previous treatment failure with pegylated interferon + ribavirin; PR: pegylated interferon + ribavirin; SOF: sofosbuvir; wk: weeks; DCV: daclatasvir; SIM: simeprevir; RBV: ribavirin; LDV: Ledipasvir

Table 9. Treatment outcomes for genotype 4 patients.
Table 10. Treatment outcomes for genotype 5 or 6 patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Genotype</th>
<th>N</th>
<th>Cirrhosis</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abergel A et al.</td>
<td>SOF LDV 12 wk</td>
<td>5 treatment-naive and TF</td>
<td>41</td>
<td>Yes</td>
<td>95</td>
<td>(85)</td>
</tr>
<tr>
<td>Brown A et al</td>
<td>GZR EBR 12 wk</td>
<td>5 treatment-naive</td>
<td>8</td>
<td>No</td>
<td>63 (total) 25 100</td>
<td>(88)</td>
</tr>
<tr>
<td></td>
<td>GZR EBR RBV 12 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gane E et al</td>
<td>SOF LDV 12 wk</td>
<td>6 treatment-naive and TF</td>
<td>25</td>
<td>No</td>
<td>96</td>
<td>(80)</td>
</tr>
<tr>
<td>Zeuzem S et al</td>
<td>GZR EBR 12 wk</td>
<td>6 treatment-naive</td>
<td>10</td>
<td>Yes</td>
<td>80</td>
<td>(59)</td>
</tr>
<tr>
<td>Kwo P et al</td>
<td>GZR EBR 16 wk</td>
<td>6 TF</td>
<td>6</td>
<td>Yes</td>
<td>83 (total) 75 100</td>
<td>(89)</td>
</tr>
<tr>
<td></td>
<td>GZR EBR RBV 16 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown A et al</td>
<td>GZR EBR 12 wk</td>
<td>6 treatment-naive</td>
<td>8</td>
<td>No</td>
<td>75 (total) 75 75</td>
<td>(88)</td>
</tr>
<tr>
<td></td>
<td>GZR EBR RBV 12 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SOF: sofosbuvir; LDV: ledipasvir; GRZ: grazoprevir; EBR: elbasvir; RBV: ribavirin
8. Resistance and treatment of patients with direct-acting antiviral agent failure

An increasing number of patients will experience treatment failure with a direct-acting antiviral agent. The studies currently available have limited sample sizes to enable the efficacy and safety of second-line treatment to be correctly evaluated. This is in addition to the concept of resistance to the direct-acting antiviral agent, particularly the development of NS5A resistance-associated variants (RAVs).

8.1 Resistance to direct-acting antiviral agents

Although virological failure is very uncommon with direct-acting antiviral agents, it is a serious problem, particularly in patients with severe fibrosis or cirrhosis and requiring “salvage” therapy.

Sofosbuvir has a high barrier to resistance. The selection of sofosbuvir resistance-associated variants has been exceptionally reported and its variants rapidly disappear after discontinuation of treatment.

Protease inhibitor resistance-associated variants appear to be observed in only a minority of patients, 48 weeks after treatment failure.

The situation is different for patients exposed to an NS5A inhibitor since the selected variants display high levels of fitness and could persist for several years. A recent study showed that NS5A resistance-associated variants persisted in approximately 80% of patients 48 weeks after treatment failure (54, 100).

An observational study on resistance to direct-acting antiviral agents has been implemented in France, and it is essential to include a large number of resistant patients in this observational study so as to improve the knowledge and management of patients with resistance-associated mutations. Several therapeutic regimens from 12 to 24 weeks may be proposed; however, these have a very low level of evidence. For this reason, at the present time, the records of patients who display resistance to treatment with a direct-acting antiviral agent should be presented in multidisciplinary consultation meetings in the presence of an expert virologist.

From a virological perspective, these patients should receive further non-interferon-based treatment, containing an agent with a high barrier to resistance (sofosbuvir) and, at the very least, another agent, ideally not displaying cross-resistance to the agent administered previously.
RECOMMENDATIONS

1. In the event of treatment failure with a direct-acting antiviral agent, it is recommended that the patient’s treatment history be reviewed (compliance, drug interactions, sub-optimum regimen, premature discontinuation, etc.) (EA)

2. In the event of treatment failure with a direct-acting antiviral agent, it is recommended that resistance-associated mutations be evaluated before deciding on the new treatment line (EA)

3. It is recommended that the records of patients experiencing treatment failure with a direct-acting antiviral agent be discussed in a multidisciplinary consultation meeting with the opinion of an expert virologist (EA)

4. If possible, it is recommended that patients experiencing treatment failure with a direct-acting antiviral agent be included in cohort studies, an observational study on resistance, or therapeutic trials (EA)

8.2 Patients experiencing treatment failure with sofosbuvir + ribavirin ± pegylated interferon

According to genotype, patients experiencing treatment failure with sofosbuvir + ribavirin ± pegylated interferon may be treated with:

- Sofosbuvir + simeprevir + ribavirin for 24 weeks
- Sofosbuvir + daclatasvir + ribavirin for 24 weeks
- Sofosbuvir + ledipasvir + ribavirin for 24 weeks
- Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 24 weeks

Comments

Patients infected with HCV genotype 1.

In the study conducted by Osinusi A et al., 14 patients with genotype 1 experiencing treatment failure with sofosbuvir and ribavirin for 24 weeks received treatment with sofosbuvir + ledipasvir (39). SVR was 100%.

In a study on 51 genotype 1 patients (14 cirrhotic patients), experiencing treatment failure with sofosbuvir (25 patients experiencing treatment failure with sofosbuvir + pegylated interferon + ribavirin, 20 patients experiencing treatment failure with sofosbuvir + ribavirin, 5 patients experiencing
treatment failure with sofosbuvir placebo + pegylated interferon + ribavirin, and one patient experiencing treatment failure with GS-0938) received treatment with sofosbuvir + ledipasvir + ribavirin for 12 weeks (101). SVR was 98%. The only patient without SVR was a genotype 3a patient (included by mistake).

Patients infected with HCV genotype 2.
Two re-treatment strategies were evaluated in a small number of genotype 2 patients: Sofosbuvir + pegylated interferon + ribavirin for 12 weeks or sofosbuvir + ribavirin for 24 weeks (97). SVR was 100% (4/4) in the group with pegylated interferon and 50% (1/2) in the group without interferon.

Patients infected with HCV genotype 3.
Sixty-eight patients relapsing after treatment with sofosbuvir + ribavirin for 12 weeks were treated with the same combination for 24 weeks (97). The SVR rate was 63%, but only 47% among cirrhotic patients.
Twenty-eight genotype 3 patients having relapsed after treatment with sofosbuvir + ribavirin for 12 weeks were treated with sofosbuvir + pegylated interferon + ribavirin for 12 weeks (97). SVR was 91% (88% for cirrhotic patients).

8.3 Patients experiencing treatment failure with sofosbuvir + NS5A inhibitor

Genotype 1 or 4 patients experiencing treatment failure with daclatasvir or ledipasvir may be treated with:
- Sofosbuvir + simeprevir + ribavirin for 24 weeks.

Genotype 1 patients experiencing treatment failure with daclatasvir or ledipasvir, after also experiencing treatment failure with a first-generation protease inhibitor, should be treated based on the analysis of resistance-associated mutations.

Genotype 3 patients experiencing treatment failure with daclatasvir or ledipasvir may be treated with:
- Sofosbuvir + pegylated interferon + ribavirin for 12 weeks.

Comments
A study evaluated the efficacy of the combination sofosbuvir + ledipasvir for 24 weeks as a re-treatment strategy for 41 patients (with cirrhosis in 46% of cases) infected with genotype 1, in whom initial treatment with sofosbuvir + ledipasvir had failed (54). The patients had NS5A resistance-associated variants in 79% of cases. Previous treatment corresponded to sofosbuvir + ledipasvir ±
ribavirin (80%) or sofosbuvir + ledipasvir + GS-9669 (20%). The duration of the previous treatment was 8 weeks (73%) with the presence of resistance-associated variants in 63% of cases or 12 weeks (27%) with resistance-associated variants in all patients. Forty patients (98%) showed a virologic response at the end of treatment (1 case of breakthrough at W16). SVR4 and SVR12 were 73% and 71%, respectively. It should be noted that SVR12 was only 46% in patients for whom previous treatment for 12 weeks had failed.

8.4 Patients experiencing treatment failure with sofosbuvir + simeprevir

Patients experiencing treatment failure with sofosbuvir + simeprevir may be treated with:

- Sofosbuvir + daclatasvir + ribavirin for 24 weeks
- Sofosbuvir + ledipasvir + ribavirin for 24 weeks

Comments

At present, only a few cases of re-treatment have been reported among patients experiencing treatment failure with a second-wave first-generation protease inhibitor such as simeprevir (68).

8.5 Patients experiencing treatment failure with protease inhibitor + NS5A inhibitor + NS5B inhibitor

No studies which evaluate the re-treatment of patients experiencing treatment failure with paritaprevir/ritonavir + ombitasvir ± dasabuvir are currently available.
**RECOMMENDATIONS**

1. In the event of treatment failure with a combination of direct-acting antiviral agents, the recommended therapeutic regimen combines the following for 24 weeks (EA):
   - sofosbuvir
   - and at least one other agent from a different therapeutic class to the previous line
   - and ribavirin

2. In the special case relating to genotype 3 patients for whom treatment comprising daclatasvir or ledipasvir has failed, treatment with sofosbuvir + pegylated interferon + ribavirin for 12 weeks may be used (EA)

**RECOMMENDATION**

1. In patients experiencing treatment failure with a combination of direct-acting antiviral agents, treatment with paritaprevir/ritonavir + ombitasvir ± dasabuvir is not recommended (EA)

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**9. Treatment monitoring**

**9.1. Monitoring during treatment**

Treatment monitoring should consist of a medical appointment or therapeutic education appointment every 4 weeks to ensure treatment compliance, to evaluate potential undesirable effects and drug interactions, and, lastly, to evaluate the virological efficacy of treatment.

It is recommended that a complete blood test, blood creatinine, calculation of creatinine clearance, and liver function tests be performed at initiation of treatment and after 4 weeks of treatment. The frequency of subsequent tests should be discussed based on clinical stage. In the event of advanced fibrosis, an assessment every 4 weeks throughout the duration of treatment is recommended. When ribavirin is used, monitoring of complete blood count requires particular caution.

Evaluation of therapeutic efficacy is based on repeated measurement of viral load using tests based on real-time PCR. The same test should ideally be used to ensure the consistency of the results over time, particularly when the viral load decreases close to the limit of quantitation/detection. Evaluation
of viral load every 4 weeks during treatment enables treatment compliance and efficacy to be ensured. At the very least, the viral load should be quantified at week 4 and at the end of treatment.

**RECOMMENDATIONS**

1. A medical or therapeutic education appointment is required every 4 weeks during treatment to ensure treatment compliance, to treat possible undesirable effects, and to manage potential drug interactions (EA)

2. During treatment, evaluation of hepatitis C viral load and transaminases should be performed at 4 weeks and at the end of treatment at the very least (B)

3. When ribavirin is used, regular monitoring of complete blood count is necessary (A)

**Special case: pregnancy.**

The use of ribavirin should be accompanied by patient information on the risks in the event of pregnancy. Pregnant women should not take ribavirin during pregnancy and should not conceive in the 6 months following discontinuation of ribavirin. A pregnancy test is recommended in all women of child-bearing potential before starting treatment comprising ribavirin. The use of birth control methods is recommended throughout treatment with ribavirin and during the next 6 months for women receiving this antiviral treatment or for women whose male partner is receiving this type of treatment.

Very few data are available on direct-acting antiviral agents. Sofosbuvir has been classed in category B by the FDA; however, this situation is unclear for other direct-acting antiviral agents. Due to the short treatment duration, until other preclinical and clinical data become available, it is recommended that the same precautions be followed as for ribavirin. Likewise, no data are available with regard to breastfeeding. As a precautionary measure, if pregnancy occurs during treatment, it is recommended that treatment with the direct-acting antiviral agent be stopped. Due to the short duration of antiviral treatment, this should be planned according to liver disease severity and the patient's wish to conceive.
RECOMMENDATIONS

1. Pregnant women should not take ribavirin during pregnancy and should not conceive in the 6 months following discontinuation of ribavirin (A)
2. In the absence of preclinical data, it is recommended that direct-acting antiviral agents be avoided during pregnancy and while breast-feeding, and discontinued if pregnancy occurs during treatment (EA)

9.2 Rules relating to treatment discontinuation

Treatment should be discontinued if a suspected hepatic undesirable effect occurs:

- elevation of transaminases more than 10 times the normal limit
- elevation of transaminases less than 10 times the normal limit, but accompanied by fatigue, nausea, vomiting or jaundice, or accompanied by an elevation of bilirubin concentration, alkaline phosphatases or a reduction in prothrombin time.

Patients with an elevation of transaminases less than 10 times the normal limit, but without any symptoms at week 4, should be monitored more frequently, every week.

The persistence of a detectable low intensity viral load at week 4 or 8 of treatment is not a criterion for discontinuation (or prolongation) of antiviral treatment.

RECOMMENDATIONS

1. Antiviral treatment should be discontinued in the event of elevation of transaminases more than 10 times the normal limit (A)

RECOMMENDATIONS

1. The persistence of a detectable viral load during treatment is not a criterion for discontinuation of treatment, apart from in the presence of documented virological rebound (viral load increased by 1 log) (A)
9.3 Monitoring after treatment discontinuation

9.3.1. Virological monitoring

It is necessary to have information on viral load at the end of treatment to be able to distinguish virological breakthrough from post-therapeutic virological relapse. Among patients with an undetectable viral load at the end of treatment, the risk of virological relapse is very low (< 10%). To ensure complete viral elimination, viral load should be determined by real-time quantitative PCR 12 and 48 weeks after discontinuation of treatment. In the absence of abnormal liver function tests and/or risk factors for viral exposure, the test for viral RNA is no longer necessary. After SVR, the activity of hepatic lesions related to HCV is interrupted; however, monitoring should be maintained in the event of risk factors for metabolic and/or alcoholic liver disease.

In patients with fibrosis F3 or F4, the risk of developing hepatocellular carcinoma decreases significantly relative to patients maintaining detectable viral replication, but warrants continued six-monthly ultrasonographic monitoring. Studies are still necessary to determine the duration of monitoring. In patients presenting oesophageal varices before treatment, treatment and monitoring of portal hypertension should be adapted to each patient.

Certain patients have a detectable but unquantifiable viral load at the end of treatment (102). This result should not cause antiviral treatment to be prolonged beyond the initially envisaged treatment duration, and is not predictive of failure. Likewise, certain patients have a slightly quantifiable viral load at the end of treatment. In this case once again, this result should not cause antiviral treatment to be prolonged beyond the initially envisaged treatment duration, and is not predictive of failure.

9.3.2. Special situations

In patients who still have a risk factor for exposure to the hepatitis C virus, it is recommended that the absence of viral re-infection be checked annually or, in the event of abnormal liver function tests, by determining viral load by PCR, particularly among drug users and MSM.

In patients experiencing failure of antiviral treatment with direct-acting antivirals, monitoring of liver disease depends on the stage of progression of liver disease before treatment. In all cases, an evaluation of the liver function tests and complete blood count is recommended every 12 months. In the event of extensive fibrosis F3 or F4, screening for hepatocellular carcinoma by abdominal ultrasonography is recommended every 6 months, and endoscopic monitoring of oesophageal varices is recommended in the event of cirrhosis.
Prospective evaluation of recurrence of hepatitis C virus infection in patients with sustained virologic response and receiving immunosuppressant therapy is not recommended in routine practice.

**RECOMMENDATIONS**

1. Measurement of hepatitis C viral load should be performed 12 and 48 weeks after discontinuation of treatment (A)
2. Screening of hepatocellular carcinoma by six-monthly abdominal ultrasonography should be continued in patients with severe fibrosis or cirrhosis regardless of response to treatment (A)
3. Monitoring of portal hypertension depends on the pre-treatment situation and should be adapted on a case-by-case basis (EA)
4. In the event of sustained virological response, monitoring of hepatitis C viral load is recommended in patients who remain exposed to viral infection (A)
5. In the event of sustained virological response, routine virological monitoring is not necessary among patients receiving immunosuppressant therapy (EA)

**9.4 Management of side effects**

At the present time, direct-acting antiviral agents for the hepatitis C virus have a very good safety profile. The side effects described in the clinical trials and initial real-life experience do not require dose adjustment or rules for discontinuation of treatment. In the event of renal impairment, haemodialysis or drug interactions, the dosage of certain medicinal products should be adjusted.

Several cases of severe bradycardia have been described among patients receiving sofosbuvir, particularly among those receiving amiodarone. The use of treatments comprising sofosbuvir is therefore contraindicated in patients taking amiodarone. As the half-life of amiodarone is several weeks and varies according to the individual, it is wise to allow a period of at least 6 months between discontinuation of amiodarone and initiation of antiviral treatment. If antiviral treatment is necessary, non-sofosbuvir-based treatment should be preferred, under cardiological monitoring. EMEA/ANSM/FDA alerts regarding undesirable effects are regularly updated on the AFEF website (www.afef.asso.fr).

In the event of heart disease, a cardiologist's opinion is preferable before starting treatment.
When using ribavirin, if significant anaemia develops (haemoglobin < 10 g/dl), the ribavirin dose should be adjusted by reducing in 200-mg steps. A faster ribavirin dose reduction may be required in patients presenting a rapid fall in haemoglobin concentration. Administration of ribavirin should be discontinued if haemoglobin concentration falls below 8.5 g/dl. The use of erythropoietin is not recommended if anaemia occurs.

RECOMMENDATIONS

1. Use of the combinations sofosbuvir + daclatasvir and sofosbuvir + ledipasvir is contraindicated in patients taking amiodarone (A)

9.5 Management of drug interactions

Sofosbuvir gives rise to very few drug interactions. The use of NSSA inhibitors or protease inhibitors, ritonavir-boosted or not, exposes patients to multiple drug interactions which can be found on the following website http://www.hep-druginteractions.org/. It is necessary to evaluate the potential drug interactions before starting antiviral treatment in order to adapt the dosages of each medicinal product. Furthermore, drug assays may be performed in order to manage these interactions throughout the duration of antiviral treatment and/or in situations involving renal impairment with or without haemodialysis. Nevertheless, management of these interactions is facilitated by the short duration of antiviral treatment.

In practice, it is necessary to list all medicinal products taken (not forgetting self-medication) before and during treatment. In the event of a potential drug interaction, it is necessary to assess whether the medicinal product in question is truly necessary, or if it may be discontinued during antiviral treatment, or if its dosage can be adjusted so as to allow antiviral treatment. This highlights the importance of multidisciplinary management, particularly with the assistance of a pharmacist.
RECOMMENDATIONS

1. Multiple interactions between direct-acting antiviral agents and certain medicinal products have been described. It is recommended that all potential interactions between antiviral treatment for hepatitis C and the patient’s usual treatment be evaluated via the website www.hep-druginteractions.org (A)

2. When introducing a new medicinal product during antiviral treatment, the potential interactions must be evaluated (A)

3. Renal function should be monitored during treatment with sofosbuvir (B)

10. Therapeutic education

10.1. Introduction

The objective of therapeutic education is to place the patient him/herself at the very centre of management in order to improve his/her autonomy, experience and adherence, not only to drug treatment, but also to the overall therapeutic project, taking into account the comorbidities, psychosocial support and quality of life. Therapeutic education improves patient adherence to treatment and, perhaps, recovery without significantly increasing the cost of management owing to the resulting reduction in the number of further treatments (103).

10.2. Why therapeutic education?

The different arguments in favour of education programmes during management of hepatitis C are as follows:

- chronic hepatitis C is a potentially fatal but curable disease

- viral eradication enables the morbidity and mortality of this infection to be considerably reduced

- we have access to effective treatments, compliance with which is a major challenge (this treatment gives rise to undesirable effects and potential drug interactions liable to limit treatment adherence).
Moreover, therapeutic education programmes enable lifestyle measures to be set in place to prevent the transmission of the viral infection and exacerbation of liver disease by fighting against comorbidities before negativation of viral replication but also after recovery.

10.3. Legislative framework

Therapeutic education has been described in the certification manual for healthcare establishments since 2008. Since the French "HPST" law of 21 July 2009, therapeutic education has been a part of patient rights. This should be:

- accessible to all patients, regardless of their location of social conditions
- based on the principle of delegation of assignments
- independent from the pharmaceutical industry
- organised in a specific framework, following a programme approved by the Regional Health Agency (ARS) involving a partnership between a team of healthcare professionals including attending physicians, patients and patient associations. The protagonists involved in therapeutic education should have received specific training (recognised qualification). The programmes should undergo annual self-evaluation by the team and evaluation every 4 years by the ARS in order to obtain renewable approval. This approval does not, however, constitute a source of funding.

10.4. Implementation of therapeutic education

Therapeutic education consists of 3 phases:

1. Pre-treatment phase
   After initial contact between the carer and the patient, this phase should comprise an evaluation of the patient's level of knowledge which needs to be broadened in order to have a proper understanding of the disease, the methods for limiting viral transmission and factors (alcohol, excessive weight, etc.) liable to exacerbate liver fibrosis. Therapeutic education should also consider the practical aspects of management: location and function of teams, role of each protagonist involved in management, therapeutic options (available treatments, efficacy and safety, constraints). It should enable specific goals to be defined with the patient.
This step, of key importance, enables patients to accept their illness more readily, and to identify the different determining factors which will motivate them to accept the healthcare process. It assesses their needs while taking into account patient characteristics, socioprofessional and family environment, any comorbidities liable to accelerate progression of fibrosis and cirrhosis and/or reduce the chances of SVR (including addictions, coinfections, and metabolic risk factors which may require dietetic management), their usual treatments (to evaluate potential drug interactions) and their requirements.

2. Treatment phase
This phase involves support throughout treatment, evaluation of its efficacy and safety, together with its impact on the socioprofessional and family environment and on patient quality of life.

3. Post-treatment phase
This phase is essential in order to ensure patient virological cure, management of other comorbidities (known or not, sometimes exacerbated after treatment), and the overall improvement in patient quality of life. After SVR, psychological support should continue in order to avoid the patient feeling abandoned by the care team. In cirrhotic patients, steps should be taken to ensure that the patient understands the importance of continuing routine screening for complications, particularly hepatocellular carcinoma and to ensure that he/she remains motivated. It is essential to emphasise, with the patient and medical contacts, the fact that the annual risk of hepatocellular carcinoma decreases after virological eradication but is not eliminated, particularly in the event of a persistent comorbidity (alcohol use or metabolic abnormalities related to excessive weight). The post-treatment phase is important in the event of relapse (this risk should be explained to the patient regularly before and during treatment) in order to manage the psychological consequences and propose a new therapeutic solution.

10.5. Therapeutic education team
Therapeutic education is based on a multidisciplinary approach. It includes:

- the patient him/herself, as patients are involved in drawing up the therapeutic education programme, and patient experts

- the following healthcare professionals, according to patient profile:
- the hepatogastroenterologist in charge of the patient

- the nurse, who is often the pivotal and first contact between the patient and the therapeutic education team (identification of needs following an interview with the patient, nurse diagnosis, determination of healthcare goals, implementation and adaptation of appropriate action). This may involve nurses practising in a hospital or community environment (particularly for patients living a long way from the hospital)

- the attending physician whose roles vary according to his/her contribution and availability (first recourse, longitudinal follow-up and contact with family members, overall patient follow-up, application for 100% reimbursement, healthcare coordination, upkeep of records and prevention)

- the social worker [evaluation of social needs, free health care for low income families (CMU), State medical aid (AME), home help if necessary, or, indeed, a medicalised apartment for the most vulnerable individuals]

- the pharmacist (information on current treatments and drug interactions)

- the psychologist or psychiatrist (guidance and psychological support, management of certain comorbidities including addictions or concomitant psychiatric disorders)

- the dietician in the event of nutritional problems (excessive weight, or, on the contrary, undernutrition)

- the addiction specialist in the event of addictions

- the infectious diseases specialist for HIV-coinfected patients

- patient associations

Participation in these programmes requires the therapeutic education team to work on certain skills (listening, communication, human relations, teaching, leadership ability, methodology, organisation, development of written resources, entertaining if possible—questionnaires, brochures, or films, ability to adapt the programmes and resources based on therapeutic progress, the availability of new agents and possibilities for reimbursement according to the characteristics of each patient).

Lastly, one of the major obstacles to broadly implementing therapeutic education is the lack of funding.
10.6. Therapeutic education in the era of direct-acting antiviral agents

Therapeutic education in the era of direct-acting antiviral agents includes certain specific features. The fact that the new highly effective therapeutic combinations are better tolerated and prescribed for shorter periods than the former treatments could suggest a lesser need for therapeutic education. In fact the opposite is true, the new characteristics of these combinations, and the characteristics of patients able to benefit from this, increase the need for therapeutic education all the more.

Several points should be highlighted regarding the specific characteristics of treatment.

- Due to the high efficacy of the treatments, compliance is a major therapeutic challenge
- The existence of drug interactions requires knowledge of ongoing treatments and assurance that the patient has understood the need to contact the prescribing department if any new medication or self-medication is prescribed
- It is important to explain to the patient that concomitant intake of certain non-medicinal substances is prohibited, such as grapefruit or blood orange juice, and, in certain cases, St John's Wort
- Dispensing of treatment, exclusively on a monthly basis in the public or private hospital pharmacy, also requires a schedule to be drawn up with the patient to ensure that he/she can obtain the treatments regularly
- Owing to the limited hindsight available since marketing authorisation (MA) was obtained for direct-acting antiviral agents, the absence of rare or serious undesirable effects not reported during pre-registration studies cannot be confirmed.

The benefit of therapeutic education on the efficacy of combinations using direct-acting antiviral agents should be rapidly evaluated.

**RECOMMENDATIONS**

1. Therapeutic education should be proposed for all patients, and adapted to their profile, including those awaiting treatment and those displaying sustained virological response (EA)
2. Specific budgets are necessary for the successful implementation of therapeutic education in hepatitis C (EA)
3. The benefit of therapeutic education in the therapeutic management of hepatitis C using direct-acting antiviral agents should be evaluated (EA)
11. Monitoring of compliance

Thorough implementation of antiviral treatment enables very high SVR rates to be achieved. In contrast, sub-optimum use of the prescribed treatment exposes patients to reduced levels of efficacy, mainly due to relapses, but may also give rise to breakthrough and the emergence of resistance-associated variants (43). Hence, simple measures aiming to optimise treatment adherence should be set in place.

Before starting antiviral treatment, patients should be informed of its chronological implementation, and its undesirable effects, even for short-term regimens not containing interferon. Information on the prevention or treatment of these undesirable effects is required. Follow-up appointments and/or telephone contact should be scheduled in order to assess the degree of compliance and to manage any undesirable effects. This contact will also make it possible to verify maintenance of the prescribed dosages, the proper management of missed doses, the absence of additional risks of pharmacological interactions, etc. A patient reminder procedure is helpful if appointments are missed. Quantitation of viral load after 4 weeks of treatment may be helpful in confirming treatment compliance.

Management and treatment of chronic hepatitis C should be optimised in a multidisciplinary manner, involving clinical practitioners, nurses, addiction specialists, pharmacists and psychosocial professionals, in the context of overall health education. Other measures may increase treatment compliance and the quality of clinical management in certain patients: intervention by therapeutic education nurses, translator support for foreign patients, or support from patient associations.

Alcohol use has a negative effect on treatment compliance in studies involving interferon; however, no data are available concerning direct-acting antiviral agents. Persistent alcohol use is not a contraindication to treatment, but warrants multidisciplinary management, notably in order to ensure treatment compliance, adherence in terms of follow-up and also to help control possible addiction (104).
12. Monitoring of patients with sustained virological response

Sustained virological response 12 weeks (SVR12) after treatment is correlated with maintenance of this response at 24 weeks with positive and negative predictive values > 99% (105). SVR at 12 weeks is therefore a good treatment efficacy endpoint.

Non-cirrhotic patients having achieved SVR should undergo a test for viral RNA 48 weeks after the end of treatment. If RNA is undetectable, eradication may be considered final, and subsequent control is not necessary. Patients presenting comorbidities which could have a hepatic impact (alcohol use, diabetes, metabolic syndrome) should continue to undergo regular monitoring.

Cirrhotic patients with SVR should have a test for viral RNA 48 weeks after stopping treatment and should undergo continued screening for HCC, even if the risk of HCC is lower relative to patients without SVR (13). The duration of ultrasonographic screening for HCC has not been defined as certain studies demonstrate the persistence of HCC risk several years after SVR. Oesophageal varices existing
prior to treatment should also be monitored. The presence of cofactors for hepatic morbidity (alcohol, diabetes, metabolic syndrome) also warrants continued specific management.

Persistent at-risk behaviour (active drug users, at-risk sexual behaviour) exposes patients to the risk of re-infection with an estimated incidence of between 1% and 5% per year (106, 107). Screening for re-infection requires tests for viral RNA due to the persistence of anti-HCV antibodies in the majority of patients having achieved SVR after treatment. A test for viral RNA is also recommended in the event of hepatic cytolysis occurring after SVR.

Monitoring of patients with SVR should take PRO (patient reported outcomes) into account. The impact of SVR in patients should take into account their quality of life (particularly fatigue and anxiety-depressive syndromes) (108). Several questionnaires may be used: CLDQ-HCV (Chronic Liver Disease Questionnaire-HCV), SF-36 (Short Form-36), FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue), WPAI: SHP (Work Productivity and Activity Index: Specific Health Problem). These criteria improve after treatment, particularly with sofosbuvir + ledipasvir (10).

**RECOMMENDATIONS**

1. **After SVR, patients without severe fibrosis or cirrhosis and without hepatic comorbidities (alcohol use, metabolic syndrome) no longer require special monitoring if their transaminase levels are normal, with undetectable viraemia 48 weeks after stopping treatment (B)**

2. **After SVR, patients with severe fibrosis or cirrhosis should undergo long-term monitoring (screening for hepatocellular carcinoma, monitoring of portal hypertension) (A)**

3. **After SVR, patients involved in at-risk practices (active drug users, at-risk sexual behaviour) should be informed of the risk of re-infection and undergo an annual test for HCV-RNA (A)**
13. Treatment of patients with severe liver disease

13.1. Compensated cirrhosis

Numerous studies and meta-analyses have shown that SVR in patients with compensated cirrhosis was associated with a significant reduction in the incidence of decompensated cirrhosis and hepatocellular carcinoma (14). However, SVR rates are generally lower, even with the new direct-acting antiviral agents, in cirrhotic patients than in patients with mild or moderate fibrosis. In the event of a 12-week treatment strategy comprising ribavirin, it can sometimes be difficult to maintain in these patients. If ribavirin is discontinued, treatment should be extended until week 24. Overall management of patients suffering from severe liver disease, who are often elderly and present comorbidities, requires regular monitoring, particularly of potential undesirable effects arising from treatment for hepatitis C. The therapeutic strategy should be adapted to HCV genotype, avoiding the use of interferon. SVR does not completely eliminate the risk of hepatocellular carcinoma, which necessitates continued screening, as recommended according to good clinical practice.

**RECOMMENDATIONS**

1. All patients with compensated cirrhosis should be treated without delay (A)
2. If ribavirin is discontinued during a planned 12-week therapeutic strategy, treatment with the direct-acting antiviral agent should be extended until week 24 (EA)

13.2. Decompensated cirrhosis and patients awaiting liver transplantation

Liver transplantation is the treatment for decompensated cirrhosis and hepatocellular carcinoma related to chronic HCV infection. Recurrence of viral infection is constant, responsible for a reduction in graft and patient survival in the mid-term. It is therefore relevant to attempt to eradicate the viral infection prior to liver transplantation. Until now, this strategy was generally ineffective and hazardous (serious infectious complications, notably in the event of decompensated cirrhosis) with therapeutic combinations using interferon, whether treatment with pegylated interferon + ribavirin, or triple
therapy with a first-generation protease inhibitor. With the arrival of new direct-acting antiviral agents, this strategy is once again possible. Several therapeutic options are available and have been evaluated.

**Option 1**

Patients with decompensated cirrhosis and/or awaiting liver transplantation may be treated with sofosbuvir + ribavirin.

**Comments**

In an open-label, phase 2 study, 61 cirrhotic patients, on the waiting list for liver transplantation, were treated with sofosbuvir + ribavirin up to transplantation. Forty-six patients ultimately underwent transplantation, 43 of whom had an undetectable viral load at the time of transplantation. Among these 43 patients, 70% had a persistent virological response 12 weeks after transplantation, 23% presented recurrence of infection, and 3% died. In this study, duration of undetectable HCV RNA before transplantation was the best predictive factor for virological response after transplantation (33). In this study, 73% of patients presented genotype 1. Option 1 is not recommended for SVR < 90%.

**Option 2**

Patients with decompensated cirrhosis and/or awaiting liver transplantation may be treated with sofosbuvir + simeprevir ± ribavirin for 12 weeks.

**Comments**

In a US three-centre study, 147 genotype 1 patients awaiting liver transplantation were treated with sofosbuvir + simeprevir for 12 weeks, with (20 patients) or without ribavirin (127 patients). Among Child B patients, SVR was 79% without any influence arising from ribavirin (109).

In the TARGET study, 137 genotype 1 patients with decompensated cirrhosis (MELD >10) were treated with sofosbuvir + simeprevir for 12 weeks, with (29 patients) or without ribavirin (102 patients). SVR was 66 and 74%, respectively (110). Option 2 is not recommended for SVR < 90%.
**Option 3**

Patients with decompensated cirrhosis and/or awaiting liver transplantation may be treated with sofosbuvir + daclatasvir ± ribavirin for 12 weeks.

**Comments**

In the ALLY-1 study, 60 patients with decompensated cirrhosis (45 genotype 1 patients) were treated with sofosbuvir + daclatasvir + ribavirin for 12 weeks. SVR was 83% (92% in Child A patients, 94% in Child B patients, and 56% in Child C patients) (111).

In a British study, 187 patients with decompensated cirrhosis (Child ≥ 7) were treated with sofosbuvir + daclatasvir, with (172 patients) or without ribavirin (15 patients). SVR was 82% and 60%, respectively, in genotype 1 patients. SVR was 70% and 71%, respectively, in genotype 3 patients (112).

**Option 4**

Patients with decompensated cirrhosis and/or awaiting liver transplantation may be treated with sofosbuvir + ledipasvir ± ribavirin for 12 or 24 weeks.

**Comments**

In a British study, 280 patients with decompensated cirrhosis (Child ≥ 7) were treated with sofosbuvir + ledipasvir for 12 weeks, with (252 patients) or without ribavirin (28 patients). SVR was 86% and 81%, respectively, in genotype 1 patients. SVR was 59% and 43%, respectively, in genotype 3 patients (112).

In the SOLAR-2 study, 107 patients with decompensated cirrhosis (Child B7 to C12) were treated with sofosbuvir + ledipasvir + ribavirin for 12 or 24 weeks. SVR was 88% (12 weeks) and 89% (24 weeks), respectively, in genotype 1 patients. SVR was 57% (12 weeks) and 86% (24 weeks), respectively, in genotype 4 patients (113).
Option 5

Patients with decompensated cirrhosis and/or awaiting liver transplantation may be treated with grazoprevir + elbasvir for 12 weeks.

Comments

SVR was 90% in 30 genotype 1 patients presenting Child B decompensated cirrhosis treated with grazoprevir + elbasvir for 12 weeks (114).

As regards patients with decompensated cirrhosis, based on current knowledge, treatment should be discussed in expert centres. In the event of a 12-week treatment strategy comprising ribavirin, it can sometimes be difficult to maintain in these patients. If ribavirin is discontinued, treatment should be extended for 24 weeks. The effect of viral suppression on the progression of liver failure and portal hypertension has already been suggested (115), and should be confirmed in studies on a larger scale. The hypothesis that viral suppression could allow patients with decompensated cirrhosis and without cancer to be taken off the waiting list should be validated by means of studies. This has only been validated in a single clinical case to date (116).
RECOMMENDATIONS

1. In patients with decompensated cirrhosis, if ribavirin is discontinued during a planned 12-week therapeutic strategy, treatment with the direct-acting antiviral agent should be extended until week 24 (EA)

2. The following therapeutic options are recommended for patients with Child B cirrhosis:
   - Sofosbuvir + daclatasvir + ribavirin for 12 weeks in genotype 1 (B) or genotype 4 patients (C)
   - Sofosbuvir + daclatasvir for 24 weeks in genotype 1, 2 and 4 patients (EA)
   - Sofosbuvir + daclatasvir + ribavirin for 24 weeks in genotype 3 patients (EA)
   - Sofosbuvir + ledipasvir + ribavirin for 12 weeks in genotype 1 patients (B)
   - Sofosbuvir + ledipasvir + ribavirin for 24 weeks in genotype 1 (EA) or genotype 4 patients (C)

3. For patients on a waiting list for liver transplantation, antiviral treatment should be discussed as it is able to prevent re-infection of the graft, particularly if the viral load has been undetectable for at least a month prior to transplantation (A)

4. Patients with preserved liver function (Child A) should be able to benefit from the combinations of direct-acting antiviral agents used in cirrhotic patients (A)

5. Treatment is recommended for patients with hepatocellular carcinoma and a MELD score < 12 (EA)

6. Treatment is recommended for patients with intermediately severe cirrhosis (MELD < 20) without hepatocellular carcinoma as viral suppression could enable planned transplantation to be suspended (EA)

7. Treatment should be discussed on a case-by-case basis for patients with severe cirrhosis without hepatocellular carcinoma with a MELD score > 20 (EA)

8. For patients with hepatocellular carcinoma in the context of decompensated cirrhosis (MELD > 12), antiviral treatment could delay transplantation by improving the MELD score. The indication for this treatment should be discussed in consultation with the transplantation team (EA)
13.3. Recurrence after liver transplantation

Recurrence of hepatitis C virus infection is constant after liver transplantation and the rate of progression of fibrosis is accelerated. Approximately one-third of patients develop severe fibrosis within 5 years following transplantation. Furthermore, serious forms of recurrence also exist, known as cholestatic fibrosing hepatitis which progress in the short term towards either re-transplantation, or death. For all of these reasons, patients undergoing transplantation for liver disease related to HCV should be treated as a priority. Several therapeutic options are available and have been evaluated (Table 12).

**Option 1**

After liver transplantation, patients may be treated with sofosbuvir + ribavirin for 24 weeks.

**Comments**

In the 2 main studies which analysed the results of the combination sofosbuvir + ribavirin in predominantly genotype 1 patients post-transplantation and having received previous treatment before or after transplantation, SVR was 59 to 70%, according to the severity of recurrence (117, 118). Option 1 is not recommended for SVR < 90%.

**Option 2**

After liver transplantation, patients may be treated with sofosbuvir + daclatasvir ± ribavirin for 12 to 24 weeks.

**Comments**

A study which was part of the ALLY-1 trial reported the results of the combination sofosbuvir + daclatasvir + ribavirin for 12 weeks in 53 patients post-transplantation, including 41 genotype 1 patients. SVR was 94% (111).

A study which was part of the ANRS CUPILT cohort reported the results of the combination sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks in 130 patients post-transplantation, including 107 genotype 1 patients. SVR was 93% (treatment for 12 weeks) and 97% (treatment for 24 weeks) (119).
**Option 3**

After liver transplantation, patients may be treated with sofosbuvir + ledipasvir + ribavirin for 12 or 24 weeks.

**Comments**

A study which was part of the SOLAR-2 trial reported the results of the combination sofosbuvir + ledipasvir + ribavirin for 12 or 24 weeks in 168 patients post-liver transplantation, including 147 genotype 1 patients and 21 genotype 4 patients, presenting compensated F0-F4 recurrence. SVR was 95% (treatment for 12 weeks) and 98% (treatment for 24 weeks) (113).

**Option 4**

After liver transplantation, patients may be treated with paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks.

**Comments**

Treatment with paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin was evaluated in 34 genotype 1 patients post-liver transplantation presenting moderate viral recurrence (≤ F2) more than 1 year post-transplantation (120). SVR was 97%. The tacrolimus doses had to be adjusted due to drug interactions.

To summarise, the strategies used in non-transplant patients are probably also effective in post-transplantation patients. Potential interactions with immunosuppressant medication, particularly drugs that inhibit the metabolism of calcineurin inhibitors, should be taken into account. Furthermore, the use of ribavirin exposes patients to an increased risk of anaemia (impaired renal function, low baseline haemoglobin, mycophenolate). The optimum time of treatment has yet to be determined (immediately after transplantation or according to the development of hepatic fibrosis?).
RECOMMENDATIONS

1. Liver transplant patients are among the priority populations to be treated owing to the early onset and severity of lesions induced by recurrence of HCV infection (A)
2. The strategies used should be adapted to HCV genotype (A)
3. The choice of strategy should take into account the specific characteristics of post-transplantation patients: drug interactions with immunosuppressants, exacerbated risk of anaemia with ribavirin use, frequently impaired renal function (B).
4. The preemptive treatment strategy for recurrence of HCV in the graft should be evaluated in clinical studies (EA)

RECOMMENDATIONS

1. Treatment with sofosbuvir + simeprevir is not recommended for post-liver-transplantation patients (A)
2. Due to drug interactions, first-line treatment with paritaprevir/ritonavir + ombitasvir ± dasabuvir is not recommended for post-liver-transplantation patients (A)

Table 12. Results of studies in post-liver-transplantation patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Genotype 1 (%)</th>
<th>N</th>
<th>Cirrhosis (%)</th>
<th>SVR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlton M et al.</td>
<td>SOF RBV 24 wk</td>
<td>82</td>
<td>40</td>
<td>40</td>
<td>70</td>
<td>(118)</td>
</tr>
<tr>
<td>Forns X et al.</td>
<td>SOF PR 24-48 wk</td>
<td>82</td>
<td>104</td>
<td>50</td>
<td>59</td>
<td>(117)</td>
</tr>
<tr>
<td>Kwo PY et al.</td>
<td>3D RBV 12 wk</td>
<td>100</td>
<td>34</td>
<td>No</td>
<td>97</td>
<td>(120)</td>
</tr>
<tr>
<td>Pungpapong S et al.</td>
<td>SOF SIM ± RBV 12 wk</td>
<td>100</td>
<td>109</td>
<td>29 (F3F4)</td>
<td>91</td>
<td>(121)</td>
</tr>
<tr>
<td>Brown et al. TARGET</td>
<td>SOF SIM ± RBV 12 wk</td>
<td>100</td>
<td>68</td>
<td>54</td>
<td>90</td>
<td>(122)</td>
</tr>
<tr>
<td>Reddy KR et al.</td>
<td>SOF LDV RBV 12-24 wk</td>
<td>99</td>
<td>223</td>
<td>50</td>
<td>88</td>
<td>(123)</td>
</tr>
<tr>
<td>Coilly A et al. CUPILT</td>
<td>SOF DCV ± RBV 24 wk</td>
<td>82</td>
<td>130</td>
<td>30</td>
<td>96</td>
<td>(119)</td>
</tr>
<tr>
<td>Manns M et al.</td>
<td>SOF LDV RBV 12-24 wk</td>
<td>87</td>
<td>168</td>
<td>NA</td>
<td>94-98</td>
<td>(113)</td>
</tr>
<tr>
<td>Poordad F et al.</td>
<td>SOF DCV RBV 12 wk</td>
<td>77</td>
<td>53</td>
<td>NA</td>
<td>94</td>
<td>(111)</td>
</tr>
</tbody>
</table>

PR: pegylated interferon + ribavirin; SOF: sofosbuvir; wk: weeks; DCV: daclatasvir; SIM: simeprevir; RBV: ribavirin; LDV: ledipasvir; 3D: paritaprevir/ritonavir + ombitasvir + dasabuvir
14. Treatment in special populations

14.1. Patients coinfected with HBV

HBV (± HDV) coinfection should be routinely investigated in HCV-infected patients. In the event of HCV-HBV coinfection, the indication for antiviral treatment for hepatitis C should be discussed regardless of liver fibrosis, as the progression of liver disease to severe fibrosis or cirrhosis is faster than in patients with HCV mono-infection (124). In inactive carriers of the HBs antigen, the risk of hepatitis B virus reactivation should be taken into account at the time of or shortly after eradication of the hepatitis C virus. In patients treated for hepatitis B, there is no interaction between tenofovir or entecavir and direct-acting antiviral agents. Owing to the potential nephrotoxicity of tenofovir and ledipasvir, monitoring of renal function during combination is a precaution for use.

**RECOMMENDATIONS**

1. HBV coinfection should be routinely investigated in all patients infected with HCV (together with HDV in the event of proven HBV coinfection) (A)
2. Treatment of hepatitis C should take place regardless of liver fibrosis (A)
3. Among inactive carriers, HBV replication should be monitored during and after treatment of hepatitis C in order to detect and promptly treat reactivation of the hepatitis B virus sometimes associated with eradication of the hepatitis C virus (A)

14.2. Patients with severe renal impairment or on haemodialysis

HCV infection is common among haemodialysis patients. This is associated with an increased risk of all-cause mortality and mortality related to liver disease. After kidney transplantation, hepatic lesions may become exacerbated due to immunosuppression. For this reason, haemodialysis patients, particularly candidates for kidney transplantation, should receive antiviral treatment for hepatitis C. The use of ribavirin may be problematic in this patient population owing to the risk of anaemia. A dosage of 200 mg/day or every 2 days or 200 mg 3 times a week, after dialysis is recommended. Several options are available for the treatment of haemodialysis patients.
Option 1. Treatment with sofosbuvir + ribavirin

The major metabolite of sofosbuvir, GS 331007, is eliminated via the kidney (125). Ten patients infected with genotype 1 or 3 suffering from severe renal impairment (creatinine clearance < 30 ml/min, Cockcroft-Gault formula), but not on dialysis, were treated with sofosbuvir 200 mg/day and ribavirin 200 mg/day for 24 weeks. SVR was 40%. No virologic breakthrough was observed. The viral kinetic profile was similar to that observed in 114 patients with normal renal function. GS 331007 and sofosbuvir blood concentrations were 4 times higher and slightly higher, respectively, in the event of renal impairment, than in a control group infected with HCV and receiving sofosbuvir 400 mg/day. No relationship was observed between the sofosbuvir or GS 331007 concentrations and SVR. Other than anaemia, no major undesirable effects, particularly cardiac effects, occurred. Option 1 is not recommended for SVR < 90%.

Option 2. Treatment with sofosbuvir + simeprevir

In a pilot study, 4 patients infected with genotype 1 (2 cases of cirrhosis, 1 case of cholestatic fibrosing hepatitis, 1 case of severe acute kidney rejection in a liver-kidney transplant patient) presenting severe renal impairment were treated with the combination sofosbuvir 400 mg every 2 days + simeprevir 150 mg per day (3 patients) or ribavirin 200 mg every 2 days. Three out of 4 patients presented SVR. No virologic breakthrough was observed, and there were no treatment discontinuations due to severe adverse reactions (126). Sofosbuvir could be administered at a dose of 400 mg every 2 days for patients with severe renal impairment.

The pharmacokinetic profile of simeprevir was evaluated in 8 patients with severe renal impairment (moderate creatinine clearance MDRD 19.7 ml/min) and compared with that observed in 8 subjects with normal renal function. Following a single dose of 150 mg simeprevir, exposure to the drug was 62% higher than in healthy subjects. Renal impairment did not modify the fraction bound to proteins. Simeprevir was well tolerated in the event of renal impairment. No dose adjustment was necessary in patients with severe renal impairment. These results were presented at the 8th International Workshop on Clinical Pharmacology of Hepatitis Therapy (Cambridge, MA, USA June 26 – 27 June, 2013).

Recently, 17 patients infected with genotype 1 undergoing dialysis or presenting creatinine clearance < 30 ml/min were treated with sofosbuvir 400 mg per day + simeprevir 150 mg per day for 12 weeks
SVR was observed in 11 patients who reached follow-up at 12 weeks after discontinuation of treatment. No treatment discontinuations occurred.

Nineteen patients (11 patients with cirrhosis) infected with genotype 1 presenting end-stage renal failure (creatinine clearance MDRD < 15 ml/min or on dialysis) were treated with sofosbuvir 400 mg every 2 days (3 patients) or 200 mg per day (16 patients) + simeprevir 150 mg per day for 12 or 24 weeks (128). Treatment was well tolerated and SVR was 88%

In the TARGET cohort, 10 patients with severe renal impairment (glomerular filtration rate < 30 ml/min) were treated with sofosbuvir + simeprevir without dose adjustment. SVR was 80%. Compared to non-renally impaired patients, renally impaired patients more frequently presented anaemia, deterioration of renal function and more severe adverse reactions without an increase in premature discontinuation for adverse reactions. These results suggest that this treatment may be used in renally impaired patients subject to intensified monitoring (129).

Option 3. Treatment with sofosbuvir + daclatasvir

Exposure to daclatasvir is increased 1.3-fold, 1.6-fold and 1.8-fold in patients who present creatinine clearance (MDRD method) of 60, 30 and 15 ml/min, respectively, relative to subjects with normal renal function. There is no relationship between peak daclatasvir concentration and creatinine clearance. Daclatasvir may be administered in the event of renal impairment, without dose adjustment. These results were presented at the 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy (Washington DC, May 19–21, 2014).

Option 4. Treatment with sofosbuvir + ledipasvir

Renal elimination of ledipasvir is low (1%). The pharmacokinetics of ledipasvir were evaluated in ten patients with severe renal impairment (creatinine clearance < 30 ml/min, Cockcroft-Gault formula, range: 16.8-28.5) compared with ten control subjects with normal renal function, paired in terms of age, gender and body mass index. These patients received a single dose of ledipasvir 90 mg. Exposure to ledipasvir was similar between the 2 patient groups. Ledipasvir may administered without dose adjustment in patients with severe renal impairment (130).
Option 5. Treatment with paritaprevir/ritonavir + ombitasvir ± dasabuvir

The pharmacokinetics of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir were studied in non-HCV-infected patients, with different degrees of severity of renal impairment, after a single dose, taken under fasting conditions. Twenty-four patients were included, divided into 4 groups, according to severity of renal impairment: creatinine clearance (GFR) measured by the Cockcroft-Gault method ≥ 90 ml/min (normal renal function), between 60 and 89 (mild renal impairment), between 30 and 59 (moderate renal impairment) and between 15 and 29 ml/min (severe renal impairment). Compared to patients with normal renal function:

- patients presenting mild renal impairment did not show any variation in ombitasvir AUC; however, the AUC for paritaprevir and dasabuvir increased by 20%, and ritonavir 42%

- patients presenting moderate renal impairment did not show any variation in ombitasvir AUC; however, the AUC for paritaprevir and dasabuvir increased by 37%, and ritonavir 80%

- patients presenting severe renal impairment did not show any variation in ombitasvir AUC; however, the AUC for paritaprevir and dasabuvir increased by 50%, and ritonavir 114%.

None of these changes had an impact on treatment tolerability. Increased doses of ritonavir (200 mg instead of 100 mg per intake and per day) have already been used in treatment of HIV infection. The half-lives of direct-acting antiviral agents and ritonavir were comparable in the 4 groups, and the urinary fraction of the metabolites was unchanged ≤ 1.5%. Lastly, the fraction not bound to plasma proteins was not modified by renal impairment. These pharmacokinetic changes are not significant from a clinical perspective and suggest that there is no need for dose adjustment in renally impaired patients (131).

Recently 28 non-cirrhotic patients suffering from severe renal impairment (creatinine clearance < 30 ml/min/1.73 m², 13 of whom were on dialysis) were treated with paritaprevir/ritonavir + ombitasvir + dasabuvir for 12 weeks with (genotype 1a patients) or without (genotype 1a patients) ribavirin at a dose of 200 mg per day (132). Ten patients reached follow-up at 4 weeks after discontinuation of treatment and all had undetectable virologic results. Ribavirin was discontinued in 8/13 patients and 4 patients received erythropoietin. The pharmacokinetic data available in 17 patients were similar to those obtained for subjects without renal impairment (historical group). No severe adverse reactions were observed.
Option 6. Treatment with grazoprevir + elbasvir

The combination grazoprevir + elbasvir was evaluated in 116 genotype 1 patients with end-stage renal failure (including 77% of patients on dialysis). SVR was 99% (133). Only one relapse was observed in a genotype 1b non-cirrhotic patient. No dose adjustment was necessary, and no premature treatment discontinuations were reported.

**RECOMMENDATIONS**

1. No dose adjustment is required for patients with moderate renal impairment (creatinine clearance > 30 ml/min/1.73 m²) (A)
2. It is recommended that an opinion be sought from an expert centre for patients with creatinine clearance < 30 ml/min/1.73 m² (EA)
3. Treatment of hepatitis C is recommended for all haemodialysis patients without plans for kidney transplantation (A)
4. Therapeutic regimens not containing ribavirin are to be preferred in haemodialysis patients (A)
5. Treatment with grazoprevir + elbasvir for 12 weeks is the recommended therapeutic regimen for genotype 1 patients presenting creatinine clearance < 30 ml/min/1.73 m² (A)

14.3. Organ transplant patients

In post-kidney transplantation patients, the rate of progression of liver fibrosis is accelerated in HCV-infected patients. Hepatitis C is associated with an increase in all-cause mortality and an increase in liver-related mortality, although cardiovascular disease is the main cause of death in these patients (134). As cirrhosis is a major factor for mortality after kidney transplantation, it is recommended that the severity of liver fibrosis be evaluated in all HCV-infected renally impaired patients undergoing assessment for kidney transplantation (135). Combined liver-kidney transplantation should be envisaged for cirrhotic patients presenting portal hypertension, not responding to antiviral treatment (136). Interferon may cause rejection of the kidney and is contraindicated after kidney transplantation. The data in the literature concerning HCV infection and heart transplantation are more rare. However, deaths related to liver disease have been reported after heart transplantation in HCV-infected patients (137, 138). Very few studies have evaluated the impact of treatment with pegylated interferon + ribavirin in this population (139). However, fatal cardiotoxicity related to interferon in a heart
transplant patient has been reported (140). In this context, therapeutic regimens not containing interferon should be used in heart transplant patients.

Practically no data are available on the impact of HCV infection in lung or intestinal transplantation. HCV may increase the risk of morbidity and dysfunction of the graft in pancreatic transplantation (141).

**RECOMMENDATIONS**

1. Treatment is recommended for all organ transplant patients, regardless of the stage of liver fibrosis (EA)
2. The choice of treatment for organ transplant patients should take into account the potential drug interactions between immunosuppressants and direct-acting antiviral agents, with intensified monitoring of plasma immunosuppressant levels (A)
3. The choice of treatment should be the same as for non-organ-transplant patients (EA)

**RECOMMENDATIONS**

1. Pegylated interferon is not recommended for organ transplant patients (A)

14.4. Haemoglobin disease and haemophilia

The type of haemoglobin disease most frequently associated with hepatitis C is thalassaemia major which requires repeated transfusions. Haemophilia is also a disease frequently associated with hepatitis C as it requires repeated coagulation factor transfusions. No therapeutic studies are available concerning direct-acting antiviral agents in these patients. However, there is no reason to suggest that the efficacy or safety of direct-acting antiviral agents is different in this population compared to the populations evaluated in the therapeutic trials. However, therapeutic combinations comprising ribavirin or interferon are contraindicated due to the risk of anaemia in patients suffering from haemoglobin disease.

**RECOMMENDATIONS**

1. In patients with haemoglobin disease or haemophilia, the indications are the same as for patients not suffering from haemoglobin disease or haemophilia (A)
2. Therapeutic regimens not containing ribavirin are recommended (A)
14.5. Care personnel

The rate of transmission from infected patients to care personnel is estimated at 1.8%. Needle sticks present the highest risk of HCV transmission, mainly with intravenous needles, but sometimes also with tubular needles which, as a rule, do not contain blood.

14.6. Children and adolescents

Children mainly become contaminated with HCV by infected mothers at birth (142). Approximately 20% to 30% of them recover spontaneously before 3 years of age. Certain children born outside of France may have been contaminated via the parenteral route. The outcome is usually benign, with spontaneous recovery following post-transfusion contamination in half of children, and, usually, no advanced lesions and/or extrahepatic manifestations before the age of 35 years, in the absence of hepatic comorbidities or HIV coinfection. Follow-up is usually annual and notably includes a clinical examination and assay of transaminases. Non-invasive tests for assessment of fibrosis have been evaluated, but are not recommended by the Haute Autorité de Santé. Preventive measures include vaccination against HAV and HBV, information on the risk of alcohol use and preventive measures to avoid methods of contamination (to be explained at the time of diagnosis and to be repeated in adolescence). Treatment, the indication of which is based on clinical findings, the presence or absence of risk factors and histology, is never urgent.
RECOMMENDATIONS

1. Owing to the benign outcome during childhood in the absence of comorbidities, there is never any urgency to discuss the treatment of hepatitis C in children (A)
2. In the absence of moderate liver fibrosis or progression of hepatitis C, it is recommended to wait until adolescence or adulthood before initiating treatment for hepatitis C (EA)
3. Preventive measures should include vaccination against hepatitis A and B virus, information on the risk related to alcohol use, together with the methods of contamination and preventive measures (EA)
4. Treatment with direct-acting antiviral agents is recommended for adolescents with moderate or severe fibrosis or cirrhosis (EA)
5. Treatment should be prescribed after consultation between the hepatologists or adult and paediatric infectious diseases specialists (EA)

14.7. Drug users

In France, most new cases of contamination occur among drug users (70% of 5000 annual cases of contamination) (143). Several facilities, including drug user risk reduction support centres (CAARUD) and addiction supportive and preventive care centres (CSAPA), play a major role in terms of reducing the risks of contamination, screening for hepatitis C and access to treatment.

Drug users are at high risk of transmission owing to the high prevalence of HCV. Most cases of contamination are the result of sharing equipment and usually occur at the start of injecting. According to modelling studies, opioid substitution therapy and syringe exchange programmes were considered to have a limited impact on the prevention of hepatitis C virus spread (38). Management by means of therapeutic regimens not containing interferon, with shorter prescribing durations and better tolerability and efficacy than those containing interferon, suggests gains in terms of prolonged virological response rates, hence, in terms of the prevention of the risk of transmission of HCV (144). Thus, a recent model showed that the therapeutic management of 1% of Chicago subway drug users each year, by means of direct-acting antiviral agents, would enable a reduction in the local prevalence of HCV of almost 20% in 20 years (145). One of the preventive strategies for HCV transmission in the drug user population is therefore based on treating this population. In this population, the rate of re-infection, after viral eradication, is less than the incident rate. The efficacy of treatment with paritaprevir/ritonavir + ombitasvir + dasabuvir, with or without ribavirin, prescribed in drug users receiving opioid substitution therapy, yields SVR rates of 96% (146). The therapeutic management of drug users should ideally take place within multidisciplinary facilities in order to ensure satisfactory
compliance with treatment and limit the risk of new contamination mainly arising from continued active drug addiction (147). Furthermore, these facilities are fully suited to management of social problems and psychiatric comorbidities frequently observed. The intensified therapeutic management of drug users, including active drug addicts, seems necessary in order to reduce the number of new cases of HCV contamination (147).

Methadone and buprenorphine are not direct inducers or inhibitors of CYP enzymes (148). However, the pharmacokinetics and pharmacodynamics of substitution drugs may be affected by certain medicinal products which interact on CYP enzymes or on the P-gp drug transporter.

Sofosbuvir is a pro-drug which requires enzymatic phosphorylation in order to be active, but is not metabolised by CYP enzymes. Insofar as sofosbuvir does not alter the pharmacodynamic or pharmacokinetics of methadone, prescription thereof does not require any methadone dose adjustment in drug users (149).

Simeprevir is metabolised by the CYP3A enzyme and has an inhibitory effect (moderate) on CYP3A and CYP1A2 enzymes. However, simeprevir does not affect the pharmacodynamics or pharmacokinetics of methadone (150).

Daclatasvir is a substrate of the CYP3A enzyme, together with a substrate and inhibitor of the P-gp drug transporter. However, co-administration of daclatasvir with methadone or buprenorphine does not modify the concentration of the substitution treatment or that of the antiviral agent. Hence, daclatasvir may be prescribed without dose adjustment among drug users on methadone or buprenorphine.

Ledipasvir is an in vitro inhibitor of the P-gp drug transporter and may also be a weak enzyme inducer of the enzymes involved in metabolism, such as CYP4A4 and CYP2C. Methadone and buprenorphine concentrations may be increased in the plasma and brain during co-administration with ledipasvir.

Ritonavir is a potent inhibitor of CYP3A. Concomitant administration of paritaprevir/ritonavir + ombitasvir with or without dasabuvir and medicinal products mainly metabolised by CYP3A may give rise to an increase in the plasma concentrations of these medicinal products. Furthermore, paritaprevir, ritonavir and dasabuvir are in vitro inhibitors of the P-gp drug transporter. Co-administration of paritaprevir/ritonavir + ombitasvir + dasabuvir with buprenorphine increases buprenorphine concentrations. Adjustment of the buprenorphine dose is not recommended, but sedative state and cognitive function should be monitored in the patient in the event of co-administration. Concomitant administration of methadone and paritaprevir/ritonavir + ombitasvir + dasabuvir does not require dose adjustment.
No dose adjustment is necessary for the combination grazoprevir + elbasvir among patients treated with buprenorphine or methadone.

**RECOMMENDATIONS**

1. The use of substitution therapy does not contraindicate treatment of hepatitis C (B)
2. Treatment of all parenteral or nasal drug users is recommended in order to reduce the viral reservoir (A)
3. Treatment should be part of a general management approach: reduction in excessive alcohol use, social support, etc. (B)
4. The choice of treatment should be the same as that in the non-drug-user population (C)
5. Following SVR, patients should be informed of the risk of re-infection and undergo annual viral RNA tests for hepatitis C (A)

### 14.8. Prisoners

The prevalence of HCV in the prison population is higher than in the general population. In France, the prevalence of HCV ranges from 4.8% to 6.5% (151). The management of HCV in prison is bound by different constraints, both in terms of screening and therapeutic management (particularly regarding treatment dispensing procedures). However, therapeutic regimens not containing interferon, easier to use and allowing shorter treatment durations, should facilitate access to treatment among inmates.

**RECOMMENDATIONS**

1. Annual screening for hepatitis C is recommended for all inmates (A)
2. Treatment of all inmates is recommended in order to reduce the viral reservoir (B)
3. Non-interrupted continuation of treatment should be maintained in the event of a change in penal establishment, detention centre or release (C)
4. The choice of treatment should be the same as that in the non-prison population (C)
15. Treatment of HCV-HIV coinfected patients

15.1. Introduction

Owing to the factors for transmission shared by HIV and HCV, HIV coinfection is common and should be routinely investigated in all HCV-infected patients. Following a decline in recent years, the prevalence of coinfection is in the region of 16 to 19%. Although the incidence of HCV has decreased among drug users, who currently represent 54% to 63% of HCV-HIV coinfected individuals, the proportion of homosexual males has increased to reach 13% to 23%, due to the occurrence of sexually transmitted hepatitis C in this population since 2000 (152). The number of patients with HIV and requiring treatment in France in 2015 is estimated at between 12,000 and 15,000 (Dat AIDS data), 84% of whom correspond to genotype 1 or 4, and 53% of whom have already received treatment.

HCV-HIV coinfected individuals have two different profiles: the predominant profile involving often long-standing coinfection hence severe fibrosis or cirrhosis; and the other minority profile corresponding to more recent HCV-HIV coinfection, with earlier management of HIV infection, the use of more effective and less hepatotoxic antiretrovirals and a natural course of chronic hepatitis C similar to that observed in individuals with HCV mono-infection (1). In HCV-HIV coinfected patients, the increased risk of progression of fibrosis, which persists even after control of HIV viral load, owing to chronic inflammation and the frequent comorbidities in this context (153, 154), and the risk of transmission justify treatment of all patients.

15.2. Therapeutic options for hepatitis C in HCV-HIV coinfection

The SVR rate is similar among HCV-HIV coinfected patients and among patients with HCV mono-infection. The potential drug interactions between the combinations of direct-acting antiviral agents and antiretroviral treatments for HIV represent the main difference between HCV-HIV coinfected patients and HCV mono-infected patients. The most recent phase 3 trials showed that treatment failures, in a not insignificant number of cases, were due to repeat sexually transmitted infections.

Several therapeutic regimens have been evaluated for the treatment of HCV-HIV coinfected patients, the results of which are shown in Table 13.
15.2.1 Treatment-naive genotype 1 patients

The therapeutic regimens generally involve 12 weeks of treatment. In certain specific cases, treatment may last 24 weeks. In other cases, the addition of ribavirin may improve SVR rate. Five options without interferon are available:

- Sofosbuvir + ribavirin for 24 weeks
- Sofosbuvir + daclatasvir for 12 weeks
- Sofosbuvir + ledipasvir for 12 weeks
- Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks
- Grazoprevir + elbasvir for 12 weeks

**Genotype 1, treatment-naive, option 1**

HCV-HIV coinfected genotype 1 patients may be treated with sofosbuvir + ribavirin for 24 weeks.

**Comments**

In the PHOTON-1 and 2 studies, 226 treatment-naive patients (84% genotype 1 patients, 10% cirrhotic patients) were treated with sofosbuvir + ribavirin for 24 weeks (155) (156). Overall SVR was 81%. This was 85% for genotype 1a patients and 67% for genotype 1b patients. In the PHOTON-2 study, SVR was 64% in 22 treatment-naive cirrhotic patients. Option 1 is not recommended for SVR < 90%.

**Genotype 1, treatment-naive, option 2**

HCV-HIV coinfected genotype 1 patients may be treated with sofosbuvir + daclatasvir for 12 weeks.

**Comments**

In the randomised ALLY 2 study, 168 patients, 124 treatment-naive patients and 44 patients having experienced treatment failure (including 76% patients infected with genotype 1a, and 14% cirrhotic patients) were treated with sofosbuvir + daclatasvir. Treatment-naive patients were randomised between 12 and 8 weeks of treatment (46). SVR was 96% in patients treated for 12 weeks but only 76% in patients treated for 8 weeks. Only treatment for 12 weeks may be recommended in these patients.
**Genotype 1, treatment-naive, option 3**

HCV-HIV coinfected genotype 1 patients may be treated with sofosbuvir + ledipasvir for 12 weeks.

**Comments**

In the open-label phase 2 Eradicate study, 50 treatment-naive non-cirrhotic patients, including 78% genotype 1a patients, were treated for 12 weeks with sofosbuvir + ledipasvir (157). SVR was 98%.

In the phase 3 ION-4 study, 335 treatment-naive and treatment-experienced patients, with or without cirrhosis, were treated for 12 weeks with sofosbuvir + ledipasvir (158). SVR was 98%. 67 patients had cirrhosis in this study. SVR was 94% in the treatment-naive patients and 98% in the 47 treatment-experienced patients.

**Genotype 1, treatment-naive, option 4**

HCV-HIV coinfected, genotype 1, treatment-naive patients may be treated with paritaprevir/ritonavir + ombitasvir + dasabuvir ± ribavirin for 12 to 24 weeks.

**Comments**

In the randomised, multicentre TURQUOISE-1 study, 63 patients were included and treated for 12 weeks or 24 weeks with paritaprevir/ritonavir, ombitasvir, dasabuvir and ribavirin (1000 to 1200 mg/day according to weight) (53). 89% of patients were infected with genotype 1a and 19% had cirrhosis. SVR was 94% and 91%, respectively, for 12 and 24 weeks of treatment.

**Genotype 1, treatment-naive, option 5**

HCV-HIV coinfected, genotype 1 patients may be treated with grazoprevir+ elbasvir for 12 weeks.

**Comments**

In the C-WORTHY (phase 2) study, 59 treatment-naive, non-cirrhotic patients were treated with grazoprevir + elbasvir for 12 weeks with (n=29) or without (n=30) ribavirin (41). SVR was 97% in the presence of ribavirin and 87% in the absence of ribavirin.
In the C-EDGE study, 218 patients (86% genotype 1 patients) were treated with grazoprevir + elbasvir for 12 weeks. SVR was 95% (94.5% in genotype 1a patients and 95.5% in genotype 1b patients) (159).

15.2.2. Genotype 1 patients having experience previous treatment failure

Genotype 1 patients experiencing treatment failure with pegylated interferon + ribavirin ± first-generation protease inhibitor may be treated with:

- Sofosbuvir + daclatasvir for 12 weeks
- Sofosbuvir + ledipasvir for 12 weeks
- Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks

**Genotype 1, previously treated, option 1**

HCV-HIV coinfected genotype 1 patients having experienced previous treatment failure may be treated with sofosbuvir + daclatasvir for 12 weeks.

**Comments**

In the randomised ALLY 2 study, among the 168 patients included, 44 had experienced previous treatment failure with pegylated interferon + ribavirin and were treated with sofosbuvir + daclatasvir for 12 weeks (46). SVR was 98%. In this study, SVR was 92% in 29 cirrhotic patients.

**Genotype 1, previously treated, option 2**

HCV-HIV coinfected genotype 1 patients having experienced previous treatment failure may be treated with sofosbuvir + ledipasvir for 12 weeks.

**Comments**

In the ION-4 study, out of the 335 patients included, 185 were treatment-experienced, including 36% patients for whom treatment with a first-generation protease inhibitor had failed, were treated with sofosbuvir + ledipasvir for 12 weeks (158). SVR was 98%. 67 patients had cirrhosis in this study. SVR was 94% in the treatment-naive patients and 98% in the 47 treatment-experienced patients.
**Genotype 1, previously treated, option 3**

HCV-HIV coinfected genotype 1 patients experiencing previous treatment failure with pegylated interferon + ribavirin may be treated with paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 weeks.

**Comments**

In the randomised, multicentre TURQUOISE-1 study, 21 patients previously treated with pegylated interferon + ribavirin were treated with paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 or 24 weeks (53). 89% of patients were infected with genotype 1a and 19% had cirrhosis. SVR was 91% for 12 weeks and 100% for 24 weeks.

**15.2.3. Genotype 2 patients**

Two options without interferon are available for the treatment of HCV-HIV coinfected genotype 2 patients:

- Sofosbuvir + ribavirin for 12 to 24 weeks
- Sofosbuvir + daclatasvir for 12 weeks

**Genotype 2, option 1**

HCV-HIV coinfected genotype 2 patients may be treated with sofosbuvir + ribavirin for 12 to 24 weeks.

**Comments**

In the PHOTON-1 and 2 studies, 45 genotype 2, treatment-naive patients, including 11% cirrhotic patients, were treated with sofosbuvir + ribavirin for 12 weeks. SVR was 89% (39). In the PHOTON-1 and 2 studies, 30 treatment-experienced genotype 2 patients, including 11% cirrhotic patients, were treated with sofosbuvir + ribavirin for 24 weeks. SVR was 90% (39).
**Genotype 2, option 2**

HCV-HIV coinfected genotype 2 patients may be treated with sofosbuvir + daclatasvir for 12 weeks.

**Comments**

In the randomised ALLY 2 study, 19 treatment-naive genotype 2 patients were treated with sofosbuvir + daclatasvir for 8 or 12 weeks (46). SVR was 100%.

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### 15.2.4. Genotype 3 patients

Two options without interferon are available for the treatment of HCV-HIV coinfected genotype 3 patients:

- Sofosbuvir + ribavirin for 24 weeks
- Sofosbuvir + daclatasvir for 12 weeks

**Genotype 3, option 1**

HCV-HIV coinfected genotype 3 treatment-naive patients may be treated with sofosbuvir + ribavirin for 24 weeks.

**Comments**

In the PHOTON-2 study, 57 treatment-naive genotype 3 patients (including 3 cirrhotic patients) were treated with sofosbuvir + ribavirin for 24 weeks. SVR was 91% (156). The PHOTON-1 study showed that a treatment duration of 12 weeks was not sufficient for genotype 3 patients since, among 42 treatment-naive genotype 3 patients treated with sofosbuvir + ribavirin for 12 weeks, SVR was only 67% (155).

In the PHOTON-1 study, 17 treatment-experienced genotype 3 patients were treated with sofosbuvir + ribavirin for 24 weeks. SVR was 94% (155). The results were similar in the PHOTON-2 study (156). Forty-nine treatment-experienced genotype 3 patients were treated with sofosbuvir + ribavirin for 24 weeks. SVR was 86%. Option 1 is not recommended for SVR < 90%.
Genotype 3, option 2

HCV-HIV coinfected genotype 3 treatment-naive patients may be treated with sofosbuvir + daclatasvir for 12 or 24 weeks.

Comments

In the ALLY-2 study, 9 HCV-HIV coinfected genotype 3 treatment-naive patients were treated with sofosbuvir + daclatasvir for 8 to 12 weeks (46). SVR was obtained in 9/9 patients (100%).

In the ATU observational study on daclatasvir in HCV-HIV coinfected patients, 95 genotype 3 patients received treatment with sofosbuvir + daclatasvir for 12 to 24 weeks (160). SVR was obtained in 8/8 patients.

15.2.5. Genotype 4 patients

Three options without interferon are available for the treatment of HCV-HIV coinfected genotype 4 patients:

- Sofosbuvir + ribavirin for 24 weeks
- Sofosbuvir + daclatasvir for 12 weeks
- Sofosbuvir + ledipasvir for 12 weeks

Genotype 4, option 1

HCV-HIV coinfected genotype 4 patients may be treated with sofosbuvir + ribavirin for 24 weeks.

Comments

In the PHOTON-2 studies, 31 treatment-naive genotype 4 patients (25% cirrhotic patients) were treated with sofosbuvir + ribavirin for 24 weeks. Overall SVR was 84% (39). This was 83% in non-cirrhotic patients (19/23) and 88% in cirrhotic patients (7/8). Option 1 is not recommended for SVR < 90%.
Genotype 4, option 2

HCV-HIV coinfected genotype 4 patients may be treated with sofosbuvir + daclatasvir ± ribavirin for 12 or 24 weeks.

Comments
In the ATU observational study on daclatasvir in HCV-HIV coinfected patients, 11 genotype 4 patients were treated with sofosbuvir + daclatasvir for 12 or 24 weeks (160). SVR was 91% (88% in patients treated without ribavirin (n=8) and 100% in patients treated with ribavirin (n=3).

Genotype 4, option 3

HCV-HIV coinfected genotype 4 patients may be treated with sofosbuvir + ledipasvir for 12 weeks.

Comments
In the ION-4 study, among the 335 treatment-naive and previously treated patients, with or without cirrhosis, 8 were infected with genotype 4, and received treatment with sofosbuvir + ledipasvir for 12 weeks (48). SVR was 100%.

RECOMMENDATIONS

TREATMENT OF HEPATITIS C IS RECOMMENDED REGARDLESS OF LIVER FIBROSIS FOR HCV-HIV COINFECTED PATIENTS
1. HCV-HIV coinfected patients should be treated with the same therapeutic regimens (doses, durations, ribavirin use) as HCV mono-infected patients (A)
2. In a first-line context, owing to the drug interactions, therapeutic regimens comprising sofosbuvir + NSSA inhibitor are preferred (A)
15.3. Management of treatment for hepatitis C in HCV-HIV coinfection

15.3.1. Treatment tolerability and monitoring

The treatment discontinuation rates (0 to 3.8%) are similar among HCV-HIV coinfected patients and mono-infected patients. Monitoring of treatment efficacy and safety is identical to the procedures followed for HCV mono-infected patients. At the same time, it should be ensured that control of HIV infection is maintained during and after treatment, particularly in the event of expected interactions between direct-acting antiviral agents and antiretrovirals. Management in terms of therapeutic education by nurses trained in coinfection and involved in monitoring virologic results and assays, when these need to be prescribed, is essential. The referring departments for HIV should be capable of extending their therapeutic education resources to include monitoring of treatment for hepatitis C.

15.3.2. Virologic failure and resistance

Number of virologic failures are due to repeated sexually transmitted infections in MSM. The reinfection rate can reach 23% after 2 years of follow-up in this population (10). Hence, long-term follow-up must be planned after cure in the patient sub-groups still at risk of re-infection with HCV.

In the event of true virologic failure, and excluding sofosbuvir, HCV variants isolated at the time of failure are generally resistant to the agents used. These resistant viruses often correspond to variants already present in small quantities before treatment.

- In the study on sofosbuvir + ledipasvir in HCV-HIV coinfected patients, the only patient experiencing relapse had variants carrying a Y93H mutation in the NS5A region, the quantity of which had increased between the start of treatment, D3, and the time of relapse from 38%, to 89% and 99%, respectively (157).

- In the study on paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin in HCV-HIV coinfected patients, the two cases of virologic failure observed among 50 treated patients corresponded to cirrhotic patients who were previously non-responders and both had variants resistant to the 3 classes at the time of failure (161).

- In the study on sofosbuvir + daclatasvir in HCV-HIV coinfected patients, 16% (32/197) of strains sequenced at treatment initiation had polymorphisms in the NS5A region (codon 28, 30, 31, or 93) (162). The SVR rates were similar among patients with or without polymorphisms at treatment initiation. Among the 12 relapses, 2 had variants carrying a new mutation in the NS5A region.
15.3.3. Drug interactions

A detailed description of these interactions is available on the website http://www.hep-druginteractions.org. The recommendations for co-prescribing and dose adjustments for direct-acting antiviral agents in the presence of antiretrovirals are presented in a table which is regularly updated and available on the websites www.afef.asso.fr and www.infectiologie.com.

RECOMMENDATIONS

1. It is essential to ensure that control of HIV infection is maintained during and after treatment for hepatitis C (A)
2. It is recommended that the interactions between the antiviral agents and all medication taken by the patient be evaluated, by referring to the websites www.hep-druginteractions.org or www.afef.asso.fr or www.infectiologie.com (A)
3. Changes in antiretroviral therapy which may be necessary before initiating treatment for hepatitis C should be made in consultation with the referring physician for HIV (EA)
4. Following SVR, monitoring of viral load for hepatitis C is recommended annually in patients at risk of re-infection with the hepatitis C virus (A)

RECOMMENDATIONS

1. Discontinuation of antiretroviral therapy is not recommended when introducing treatment for hepatitis C (A)
Table 13. Treatment outcomes for HCV-HIV coinfected patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment</th>
<th>Genotype</th>
<th>N</th>
<th>Cirrhosis (%)</th>
<th>SVR (%)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Sulkowski M et al. PHOTON 1</td>
<td>SOF RBV 24 wk</td>
<td>1 treatment-naive</td>
<td>114</td>
<td>4</td>
<td>76</td>
<td>(155)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 24 wk</td>
<td>1 treatment-naive</td>
<td>112</td>
<td>15</td>
<td>85</td>
<td>(156)</td>
</tr>
<tr>
<td>Osinusi A et al. ERADICATE</td>
<td>SOF LDV 12 wk</td>
<td>1 treatment-naive</td>
<td>50</td>
<td>No</td>
<td>98</td>
<td>(157)</td>
</tr>
<tr>
<td>Sulkowski M et al. CWORTHY</td>
<td>GZV EBR ± RBV 12 wk</td>
<td>1 treatment-naive</td>
<td>59</td>
<td>No</td>
<td>93</td>
<td>(58)</td>
</tr>
<tr>
<td>Wyles D et al. ALLY 2</td>
<td>SOF DCV 12 wk</td>
<td>1 treatment-naive</td>
<td>83</td>
<td>14</td>
<td>96</td>
<td>(162)</td>
</tr>
<tr>
<td>Wyles D et al. ALLY 2</td>
<td>SOF DCV 8 wk</td>
<td>1 treatment-naive</td>
<td>41</td>
<td>14</td>
<td>76</td>
<td>(162)</td>
</tr>
<tr>
<td>Wyles D et al. ALLY 2</td>
<td>SOF DCV 12 wk</td>
<td>1 TF</td>
<td>44</td>
<td>10</td>
<td>98</td>
<td>(162)</td>
</tr>
<tr>
<td>Cooper C et al. ION 4</td>
<td>SOF LDV 12 wk</td>
<td>1</td>
<td>325</td>
<td>20</td>
<td>98</td>
<td>(158)</td>
</tr>
<tr>
<td>Sulkowski M et al. TURQUOISE 1</td>
<td>3D RBV 12 wk</td>
<td>1</td>
<td>31</td>
<td>19</td>
<td>93,5</td>
<td>(161)</td>
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<tr>
<td>Sulkowski M et al. TURQUOISE 2</td>
<td>3D RBV 24 wk</td>
<td>1</td>
<td>32</td>
<td></td>
<td>90,6</td>
<td>(161)</td>
</tr>
<tr>
<td>Rockstroh JK et al. C-EDGE</td>
<td>GZV EBR 12 wk</td>
<td>1</td>
<td>188</td>
<td>16</td>
<td>95</td>
<td>(159)</td>
</tr>
<tr>
<td>Sulkowski M et al. PHOTON 1</td>
<td>SOF RBV 12 wk</td>
<td>2 treatment-naive</td>
<td>26</td>
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<td>88</td>
<td>(155)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 12 wk</td>
<td>2 treatment-naive</td>
<td>19</td>
<td></td>
<td>89</td>
<td>(156)</td>
</tr>
<tr>
<td>Sulkowski M et al. PHOTON 1</td>
<td>SOF RBV 24 wk</td>
<td>2 TF</td>
<td>24</td>
<td></td>
<td>92</td>
<td>(155)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 24 wk</td>
<td>2 TF</td>
<td>6</td>
<td></td>
<td>83</td>
<td>(156)</td>
</tr>
<tr>
<td>Sulkowski M et al. PHOTON 1</td>
<td>SOF RBV 12 wk</td>
<td>3 treatment-naive</td>
<td>42</td>
<td></td>
<td>67</td>
<td>(155)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 24 wk</td>
<td>3 treatment-naive</td>
<td>57</td>
<td></td>
<td>91</td>
<td>(156)</td>
</tr>
<tr>
<td>Sulkowski M et al. PHOTON 1</td>
<td>SOF RBV 24 wk</td>
<td>3 TF</td>
<td>17</td>
<td></td>
<td>94</td>
<td>(155)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 24 wk</td>
<td>3 TF</td>
<td>49</td>
<td></td>
<td>86</td>
<td>(156)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 24 wk</td>
<td>3 TF</td>
<td>23</td>
<td>100</td>
<td>78</td>
<td>(156)</td>
</tr>
<tr>
<td>Molina JM et al. PHOTON 2</td>
<td>SOF RBV 24 wk</td>
<td>4 treatment-naive</td>
<td>31</td>
<td>25</td>
<td>84</td>
<td>(156)</td>
</tr>
<tr>
<td>Cooper C et al. ION 4</td>
<td>SOF LDV 12 wk</td>
<td>4 treatment-naive</td>
<td>8</td>
<td>20</td>
<td>96</td>
<td>(158)</td>
</tr>
</tbody>
</table>

SOF: sofosbuvir; RBV: ribavirin; LDV: ledipasvir; DCV: daclatasvir; GZR: grazoprevir; EBR: elbasvir; 3D: paritaprevir/ritonavir + ombitasvir + dasabuvir
16. Acute hepatitis

The majority of patients with acute hepatitis C are asymptomatic; however, the expected rate of chronic disease is extremely high, ranging from 60 to 90% according to the studies. The following factors are associated with spontaneous viral elimination: symptomatic liver disease (jaundice), female gender, young age, genotype 1, genetic polymorphism upstream from the IL28B gene. However, none of these parameters provide an accurate prediction of the chances of spontaneous resolution of viral infection on an individual scale.

16.1. Natural course

When acute hepatitis C is suspected, the diagnosis is based on the detection of anti-HCV antibodies and the viral load. Anti-HCV antibodies may appear in a delayed manner (serological window) and may be negative in the first 6 weeks after exposure to the virus. The recommendations for clinical monitoring of patients with acute hepatitis C are based on regular evaluation of liver function tests until transaminase levels return to normal and viral RNA is undetectable by PCR, suggesting spontaneous recovery. Spontaneous recovery mainly occurs within the first 6 months. Determination of recovery is based on evaluation of viral load by PCR every 4 to 8 weeks for 6 to 12 months following the first clinical symptoms. Suppression of viraemia may only be transient, and a single negative viraemia result is unable to confirm recovery. Associated viral infections should be investigated (HBV, HIV) in the event of acute hepatitis C.

Given the high rate of developing chronic disease associated with acute hepatitis C, antiviral treatment should be considered for each case. Owing to the very high efficacy and very good safety of direct-acting antiviral agents, it is reasonable to wait for at least 12 weeks after the probable date of contamination. If viral RNA is negative at week 12, monitoring should be set in place with control of viral RNA after a year, owing to the possibility of biphasic forms. If viral RNA is positive at week 24, treatment should be proposed.

In the absence of studies, in the event of exposure to the virus, preventive antiviral treatment is not recommended, owing to the low risk of transmission.
16.2. Management of acute hepatitis

During acute HCV infection, it is recommended that patients avoid hepatotoxic medications and alcohol use, and it is recommended that they take precautions to reduce the risks of transmission to others. It is recommended that patients presenting acute hepatitis C related to drug use be referred to an addiction team.

The arguments in favour of treating acute hepatitis C (before development of chronic disease) are as follows:

- High sustained virological response resulting from highly effective treatment with few undesirable effects
- Reduction in the risk of transmission of viral infection
- Prevention of the development of chronic infection and the consequences thereof, notably including hepatic fibrosis
- Prevention of the psychological repercussions of chronic infection.

However, in the treatment of acute hepatitis C virus, the efficacy and safety of treatments not comprising interferon are not yet well known.

If a decision is made to initiate antiviral treatment during the acute infection period, given the antiviral efficacy and safety profile of the new antiviral treatments, it is recommended that the same treatments be used as for chronic hepatitis C virus infection. However, in the future, based on the progress made in terms of knowledge, short-term treatments (4 to 8 weeks) may be used.

It is recommended that viral load and genotyping be performed in order to choose the most suitable therapeutic combination. Lastly, owing to their undesirable effects, the use of interferon in combination with ribavirin is no longer recommended for the treatment of acute hepatitis C even though their efficacy has been clearly demonstrated.

Therapeutic education should be combined with the therapeutic management of acute hepatitis C. In fact, it is important for patients to be informed about the methods of transmission of HCV infection and be aware of how to avoid further contamination. Patient associations and organisations working with drug users and individuals at risk play a particularly important role in this situation.
RECOMMENDATIONS

1. If acute hepatitis is suspected, investigation for viral RNA should be part of the initial work-up (A)
2. Evaluation of viral load and viral genotype is necessary in the event of a decision for treatment (A)
3. Treatment of acute hepatitis C is recommended for all patients from week 24 after the assumed date of contamination, and may be discussed as from week 12 (EA)
4. Treatment of acute hepatitis should be accompanied by measures to raise awareness concerning the reduction in the risk of contamination (EA)
5. In the event of acute hepatitis C, treatment using the same combinations of direct-acting antiviral agents without interferon as for chronic hepatitis C is recommended (EA)
6. Studies are necessary in order to evaluate the optimum therapeutic strategy (EA)

RECOMMENDATIONS

1. Treatment with pegylated interferon in combination with ribavirin is not indicated for acute hepatitis C (EA)
2. Preventive treatment for acute hepatitis C is not recommended (A)


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Declaration of interests

Prof. Olivier Chazouillères. No declarations of interests

Dr Hélène Fontaine: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck

Dr Bertrand Hanslik: Roche, Merck, Bristol Myers Squibb, Gilead, Janssen, Abbvie

Prof. Christophe Hézode: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck

Prof. Patrick Hillon. No declarations of interests

Prof. Victor de Lédinghen: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck

Prof. Georges-Philippe Pageaux: Astellas, Bristol Myers Squibb, Gilead, Merck

Dr Christophe Renou: AbbVie, Bristol Myers Squibb, Gilead, Janssen

Prof. Dominique Salmon: Bristol Myers Squibb, Gilead, Janssen

Prof. Albert Tran: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck

Prof. Fabien Zoulim: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck
# APPENDIX 1
## Programme of the Working Session on 29 May 2015

### Session 1  Moderators: D. Guyader (Rennes) – L. Serfaty (AP-HP Saint-Antoine)

**New agents & genotypes 2-3**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic classes</td>
<td>M. Bourlière (Marseille)</td>
</tr>
<tr>
<td>Virologic resistance</td>
<td>JM. Pawlotsky (APHP Henri Mondor)</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>D. Thabut (APHP Pitié Salpêtrière)</td>
</tr>
<tr>
<td>Genotype 3</td>
<td>JP. Bronowicki (Nancy)</td>
</tr>
</tbody>
</table>

### Session 2  Moderators: JP. Zarski (Grenoble) – T. Fontanges (Bourgoin-Jallieu)

**Genotypes 1 & 4**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>V. Leroy (Grenoble)</td>
</tr>
<tr>
<td>Genotype 4, 5 and 6</td>
<td>T. Asselah (APHP Clichy)</td>
</tr>
</tbody>
</table>

### Session 3  Moderators: S. Pol (APHP Cochin) – A. Pauwels (Gonnesse)

**Special populations**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Moderator</th>
</tr>
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<tbody>
<tr>
<td>Vulnerable populations (prisons, CSAPA, acute hepatitis)</td>
<td>F. Bailly (Lyon)</td>
</tr>
<tr>
<td>HCV/HIV co-infection</td>
<td>L. Piroth (Dijon)</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>JC. Duclos-Vallée (APHP Paul Brousse)</td>
</tr>
<tr>
<td>Extrahepatic manifestations &amp; kidney transplantation</td>
<td>L. Alric (Toulouse)</td>
</tr>
</tbody>
</table>

### Session 4  Moderator: S. Pol (APHP Cochin) – T Poynard (APHP Pitié Salpêtrière)

**Who should be treated in 2015?**

- For treating all patients immediately: Ph. Mathurin (Lille)
- For treatment staggered over time: Y. Yazdanpanah (AHP Bichat)
APPENDIX 2

Treatment recommendations according to patient genotype

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1 non-cirrhotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>Sofosbuvir + simeprevir (G1b)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + ledipasvir</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/r + ombitasvir + dasabuvir + ribavirin (G1a)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/r + ombitasvir + dasabuvir (G1b)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir + elbasvir</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + asunaprevir + beclabuvir + ribavirin (G1a)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + asunaprevir + beclabuvir (G1b)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + GS-5816</td>
<td>12</td>
<td>B</td>
</tr>
<tr>
<td>Previously treated PEG ribavirin ± telaprevir or boceprevir</td>
<td>Sofosbuvir + simeprevir (G1b, failure of PEG ribavirin)</td>
<td>12</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + ledipasvir</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/r + ombitasvir + dasabuvir + ribavirin (G1a failure of PEG ribavirin)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Paritaprevir/r + ombitasvir + dasabuvir (G1b failure of PEG ribavirin)</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir + elbasvir + ribavirin</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir + asunaprevir + beclabuvir (G1b failure of PEG ribavirin)</td>
<td>12</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir + GS-5816</td>
<td>12</td>
<td>B</td>
</tr>
</tbody>
</table>

| Génotype 1 avec cirrhose compensée | | | |
| Treatment-naive | Sofosbuvir + daclatasvir + ribavirin | 12 | C |
| | Sofosbuvir + daclatasvir | 24 | A |
| | Sofosbuvir + ledipasvir + ribavirin | 12 | A |
| | Sofosbuvir + ledipasvir | 24 | A |
| | Paritaprevir/r + ombitasvir + dasabuvir + ribavirin | 12 | A |
| | Grazoprevir + elbasvir + ribavirin | 12 | A |
| | Daclatasvir + asunaprevir + beclabuvir + ribavirin (G1a) | 12 | A |
| | Daclatasvir + asunaprevir + beclabuvir (G1b) | 12 | A |
| | Sofosbuvir + GS-5816 | 12 | B |
| Previously treated PEG RBV ± telaprevir or boceprevir | Sofosbuvir + daclatasvir + ribavirin | 12 | C |
| | Sofosbuvir + daclatasvir | 24 | A |
| | Sofosbuvir + ledipasvir + ribavirin | 12 | A |
| | Sofosbuvir + ledipasvir | 24 | A |
| | Paritaprevir/r + ombitasvir + dasabuvir + ribavirin (G1a failure of PEG ribavirin) | 24 | A |
| | Paritaprevir/r + ombitasvir + dasabuvir + ribavirin (G1b failure of PEG ribavirin) | 12 | A |
| | Grazoprevir + elbasvir + ribavirin | 16 | C |

<p>| Genotype 1 with Child B decompensated cirrhosis | | | |
| Treatment-naive &amp; treatment-experienced | Sofosbuvir + daclatasvir + ribavirin | 12 | B |
| | Sofosbuvir + daclatasvir | 24 | EA |
| | Sofosbuvir + ledipasvir + ribavirin | 12 | B |
| | Sofosbuvir + ledipasvir | 24 | EA |</p>
<table>
<thead>
<tr>
<th>Genotype 2</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>Sofosbuvir + ribavirin</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + ribavirin</td>
<td>12</td>
<td>C</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
<td>EA</td>
</tr>
<tr>
<td><strong>Compensated cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive</td>
<td>Sofosbuvir + ribavirin</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + ribavirin</td>
<td>24</td>
<td>C</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
<td>EA</td>
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<tr>
<td>** Decompensated cirrhosis**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + daclatasvir</td>
<td>24</td>
<td>EA</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Genotype 3</th>
<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + GS-5816</td>
<td>12</td>
<td>B</td>
</tr>
<tr>
<td><strong>Compensated cirrhosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + pegylated interferon + ribavirin</td>
<td>12</td>
<td>B</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + daclatasvir + ribavirin</td>
<td>24</td>
<td>B</td>
</tr>
<tr>
<td>Treatment-experienced</td>
<td>Sofosbuvir + GS-5816 + ribavirin</td>
<td>12</td>
<td>B</td>
</tr>
<tr>
<td>** Decompensated cirrhosis**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + daclatasvir + ribavirin</td>
<td>24</td>
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### Genotype 4

<table>
<thead>
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<th>Treatment</th>
<th>Duration (weeks)</th>
<th>Evidence</th>
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<tbody>
<tr>
<td>No cirrhosis</td>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + simeprevir</td>
<td>12</td>
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<td></td>
<td>Sofosbuvir + daclatasvir</td>
<td>12</td>
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<tr>
<td></td>
<td></td>
<td>Sofosbuvir + ledipasvir</td>
<td>12</td>
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<tr>
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<td></td>
<td>Paritaprevir/r + ombitasvir + ribavirin</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Treatment-naive</td>
<td>Grazoprevir + elbasvir</td>
<td>12</td>
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<tr>
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<td>Sofosbuvir + GS-5816</td>
<td>12</td>
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<tr>
<td>Compensated cirrhosis</td>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + simeprevir + ribavirin</td>
<td>12</td>
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<td>Sofosbuvir + simeprevir</td>
<td>24</td>
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<td>Sofosbuvir + daclatasvir + ribavirin</td>
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<td>Sofosbuvir + daclatasvir</td>
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<td>Sofosbuvir + ledipasvir + ribavirin</td>
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<td>Decompensated cirrhosis</td>
<td>Treatment-naive &amp; treatment-experienced</td>
<td>Sofosbuvir + daclatasvir + ribavirin</td>
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### Genotype 5 and 6

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<td>Sofosbuvir + daclatasvir + ribavirin</td>
<td>12</td>
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<tr>
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<td></td>
<td>Sofosbuvir + ledipasvir + ribavirin</td>
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<tr>
<td></td>
<td></td>
<td>Sofosbuvir + ledipasvir</td>
<td>24</td>
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The proposals are indicated in chronological order of the arrival of the drugs in the context of an ATU or MA.