REVIEW ARTICLE

Treatment of hepatitis C virus infection for adults and children: updated Swedish consensus guidelines 2017

Martin Lagginga, Rune Wejståla,b, Ann-Sofi Dubergc, Soo Alemand, Ola Weilandd, and Johan Westina,b; for the Swedish Consensus Group

aDepartment of Infectious Diseases, Institute of Biomedicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; bSwedish Reference Group for Antiviral Therapy (RAV), Stockholm, Sweden; cDepartment of Infectious Diseases, Örebro University, Örebro, Sweden; dDepartment of Medicine, Division of Infectious Diseases, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden

ABSTRACT

Aim: Following the approval of two new therapeutic combinations within the European Union in 2017, the former Swedish recommendations for the treatment of hepatitis C virus (HCV) infection from 2016 were deemed in need of updating.

Materials and methods: An expert meeting to this end was held in Stockholm, Sweden in October 2017.

Results and conclusions: An interferon-free combination of direct-acting antiviral agents is now recommended for all patients with chronic HCV infection, regardless of liver fibrosis stage, in order to limit morbidity and spread of the disease. An extended discussion of treatment for people who inject drugs in order to diminish transmission is included.

KEYWORDS

Hepatitis C virus
HCV
Guidelines
Direct-acting antiviral agents
Ribavirin
Genotype
People who inject drugs
PWIDs
Children
Chronic kidney disease
HIV
Elimination
Eradication
Resistance associated variants (RAVs)
Resistance associated substitutions (RASs)

ARTICLE HISTORY
Received 16 January 2018
Revised 9 February 2018
Accepted 12 February 2018

CONTACT
Martin Lagging
martin.lagging@medfak.gu.se
Department of Infectious Diseases, Institute of Biomedicine at Sahlgrenska Academy, University of Gothenburg, Guldhedsgatan 108, SE-413 46 Göteborg, Sweden

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

The World Health Organization (WHO) estimates that globally there are approximately 70–80 million humans infected with hepatitis C virus (HCV). In Sweden, the estimated prevalence is ≤0.5%, corresponding to 45,000 individuals. Approximately 2000 new cases are reported annually in accordance with the Swedish Infectious Diseases Act. Currently, intravenous drug use is the predominant route of infection in the Western world. An estimated 75% of those infected with HCV develop a chronic infection, which generally has a slow progression rate to advanced liver disease [1,2]. However, approximately 20% of those with chronic HCV infection progress to cirrhosis within 20 years from onset of infection, a proportion which tends to increase over time [3]. HCV-induced cirrhosis entails a substantial risk of serious complications such as liver decompensation including portal hypertension with oesophageal varices, ascites and hepatic encephalopathy. Furthermore, it is associated with an annual 3–4% risk of developing hepatocellular carcinoma (HCC) [4]. Chronic HCV infection has been a common indication for liver transplantation in Sweden, but after the introduction of new antiviral therapy in 2014 (Table 1), the proportion of HCV infected among liver transplant recipients has diminished. Following the approval of two new therapeutic combinations within the European Union in 2017, the former Swedish recommendations for the treatment of hepatitis C virus (HCV) infection from 2016 were updated at a recent expert meeting [5].

Acute HCV infection

Acute HCV infection spontaneously resolves within 6–12 months in approximately 25% of cases, and thus antiviral therapy can be deferred to the chronic phase.

Chronic HCV infection

The ultimate goal of the HCV treatment is to prevent cirrhosis, as this entails an increased risk of HCC and/or decompensated liver disease. The immediate virologic therapeutic objective is defined as sustained virologic response (SVR), i.e. undetectable plasma HCV RNA ≥12 weeks after end of treatment, corresponding to a cured infection.

Among HCV-infected cirrhotic patients, the annual risk of developing HCC can be reduced from approximately 4% to 1% if SVR is achieved [6]. Fibrosis stage F3 (bridging fibrosis), according to Batts and Ludwig [7] and Metavir [8], is also associated with an increased risk of HCC, and the transition from fibrosis stage F3 to F4 (cirrhosis), as well as the progression from F2 (moderate fibrosis) to F3, often is difficult to accurately diagnose, especially with non-invasive methods. Therefore, treatment should not be delayed for patients with fibrosis stages F3-4, and if possible, should be initiated before stage F3 is reached. Consequently, treatment is recommended for all patients with chronic HCV infection, regardless of liver fibrosis stage.

For patients with extrahepatic manifestations, e.g. cryoglobulin-induced vasculitis, porphyria cutanea tarda, or glomerulonephritis, antiviral therapy is warranted as soon as possible, as it generally improves these immune-mediated diseases.

In addition to reducing or abolishing the risk of HCV-induced serious liver disease and/or extrahepatic manifestations, successful treatment also eliminates the risk of transmission, for example from mother to child during pregnancy or delivery (1–5% risk), through sex, or secondary to sharing injection paraphernalia among people who inject drugs (PWIDs).

Before initiation of therapy, other factors should also be considered, such as the patient’s age, general health, overall life expectancy, own wishes, and ability to adhere to the treatment. In patients with ongoing substance abuse, where compliance problems may be anticipated, supportive care is particularly important before initiation of anti-viral treatment.

Assessment of fibrosis stage

Evaluation of the fibrosis stage should be performed in all patients with chronic HCV infection (recommendation

| Date available | Pharmaceutical | NS5B Polymerase inhibitor | NS5A Inhibitor | NS3/4A Protease inhibitor | HCV genotypes |
|----------------|----------------|---------------------------|----------------|--------------------------|--------------|
| January 2014   | Sovaldi 1 × 1  | Sofosbuvir (uridine analogue) | –              | –                        | 1–6          |
| May 2014       | Olysio 1 × 1  | –                         | –              | Simeprevir               | 1 and 4      |
| August 2014    | Daklinza 1 × 1| –                         | Daklatasvir    | –                        | 1–6          |
| November 2014  | Harvoni 1 × 1 | Sofosbuvir                 | Ledipasvir     | –                        | 1 and 4      |
| January 2015   | Viekirax 2 × 1| Ombitasvir                | Paritaprevir (+ ritonavir) | 1 and 4 |
| January 2015   | Evivira 1 × 2 | Dasabuvir (non-nucleotide) | Velpatasvir    | –                        | 1            |
| Autumn 2016    | Eproperda 1 × 1| Sofosbuvir                 | Elbasvir       | Grazoprevir              | 1 and 4      |
| August 2017    | Maviret 3 × 1 | –                         | Pibrentasvir   | Gileaprevir              | 1–6          |
| August 2017    | Vosevi 1 × 1  | Sofosbuvir                 | Velpatasvir    | Voxilaprevir             | 1–6          |
grade A1; recommendation grading scale adapted from the GRADE system used by EASL [9]). Formerly this was accomplished by means of a liver biopsy. Presently non-invasive methods such as a combination of validated blood biomarkers [10–14] and liver elasticity measurement (e.g. FibroScan®) are considered to provide a sufficient estimate [15,16]. With these methods, in particular with liver elasticity measurement, the absence of fibrosis as well as the presence of cirrhosis can be diagnosed with reasonably high accuracy. Non-invasive fibrosis evaluations utilize the same stages as a liver biopsy, e.g. the protocols suggested by Batts and Ludwig [7] and the Metavir [8], from F0 (normal liver without fibrosis) to F4 (liver cirrhosis). However, non-invasive methods are less accurate than a liver biopsy, particularly when differentiating fibrosis stages F2 and F3.

It should be noted that a liver biopsy may provide more information than simply an estimation of fibrosis stage, and can be useful if noninvasive methods render questionable results or fail, and when other causes of liver disease are suspected. An experienced liver pathologist, who can judge whether or not the material is sufficient, should perform the evaluation of the liver biopsy, and the risk of sampling error must always be considered.

Regular, biannual liver ultrasonography for surveillance of possible HCC development is recommended for cirrhotic patients, both before and after treatment (recommendation grade B2), and an endoscopy should be performed to evaluate the presence of varices. If the platelet count is above $150 \times 10^9/L$ and the liver elasticity measurement is below 20 kPa, endoscopy is often not necessary [17]. For patients with HCV-induced cirrhosis lacking varices, it is probably not necessary to perform additional gastroscopies if SVR is achieved. If and when additional gastroscopies are needed should be evaluated on an individual basis, taking into account other risk factors for progression of cirrhosis (recommendation grade C2).

### Indications for treatment

Early treatment is recommended for all patients with chronic HCV infection to reduce the risk of severe complications, stigmatization and transmission.

The World Health Organization (WHO) recently launched a global hepatitis strategy with the goal of reducing the incidence of chronic hepatitis B and C viral infection by 90%, and to reduce the mortality caused by these infections by 65% by 2030 [18]. To impact the prevalence of HCV infection, large-scale treatment of individuals at risk of transmission likely is required. This implies that PWIDs must be offered therapy. For such a treatment strategy to be successful, coordinated efforts by addiction and psychiatric clinics, social welfare services, as well as criminal justice and health care agencies to improve harm reduction in order to reduce the risk of reinfection also are required. In addition to the augmented need of treatment, increased diagnostic screening of risk groups and renewed recruitment of individuals previously diagnosed but presently lacking health care supervision also will be required. Targeted measures to address these problems are essential, and subsequently necessitate national political decisions.

Thus, it is recommended that all patients with chronic HCV infection should be treated, although patients with more advanced liver disease should be prioritized first. A large portion of patients with advanced disease has already been treated, and thus therapy should now be offered regardless of liver fibrosis stage.

### Assessment of factors influencing treatment options and the likelihood of achieving SVR

With currently available treatment options, the probability of SVR is high regardless of baseline demographics as well as clinical and virological characteristics, provided that an appropriate regimen and duration are given.

Viral genotype and the presence or absence of cirrhosis is the principal factors governing treatment recommendations:

- HCV genotype should be determined before initiating therapy because it affects the choice and duration of treatment. Additionally, re-evaluation of HCV genotype should be considered before re-treatment after relapse.
- Fibrosis stage impacts on treatment choice and duration. Markers of advanced cirrhosis (low platelet count and low albumin) as well as relapse after prior therapy impact the likelihood of achieving SVR.
- Other factors, e.g. baseline plasma viral load, may be of importance [19–21].
- Adherence to therapy is of major importance.

### Resistance against antiviral medication

Naturally occurring virus variants that entail reduced sensitivity in particular to NS5A inhibitors also may impact the likelihood of achieving SVR [22], especially for HCV genotype 1a or 3 infection. This is most evident...
for genotype 1a treated with grazoprevir/elbasvir [23]. Analysis of resistance-associated substitutions (RASs), also known as resistance-associated variants (RAVs), however, is relatively complex, can be performed with a variety of different methods yielding varying results, requires experience when evaluating, and is only available at a limited number of virological laboratories. Therefore, routine susceptibility testing is recommended only for patients with genotype 1a infection prior to therapy with grazoprevir/elbasvir, as therapy for 12 weeks without ribavirin may be given if RASs/RAVs are not detected. Alternatively, therapy may be given for 16 weeks with ribavirin if RASs/RAVs are detected or the analysis is not performed. Susceptibility testing is also recommended before retreatment of patients with decompensated cirrhosis, as protease inhibitors should not be given to Child-Pugh B or C cirrhotic patients, as well as after relapse following a second course of DAA, containing three antivirals with differing modes of action.

Prior to treatment of chronic HCV infection

Before initiating therapy, it is important that patients are well-informed, and fully understand the importance of compliance as well as monitoring. A careful review of concomitant medications is essential to avoid potential drug–drug interactions. Ribavirin is a potential teratogen, and if prescribed, the need for contraception is vital regardless of gender. Pregnancy should be avoided with all HCV treatment regimens, as experience of treatment during pregnancy is limited.

Sampling

A basic evaluation, including assessment of other causes of transaminase elevations, must be performed in accordance with local practices before initiating treatment. Prior to starting HCV therapy, the following sampling is recommended: plasma HCV RNA quantification, HCV genotyping, haemoglobin, platelet count, serum albumin, serum bilirubin, PT-INR, AST, ALT, serum creatinine to calculate creatinine-clearance, pregnancy test for fertile women, and evaluation of fibrosis stage.

Treatment of chronic HCV infection

Treatment should be initiated and monitored by clinics with experience of HCV therapy. Table 1 provides an overview of registered DAAs active against HCV infection. Combination therapy including interferon is not recommended due to an inferior safety profile, although it is still formally approved for the treatment of HCV infection. Thus, interferon-based therapy should only be given exceptionally after an individual benefit risk assessment [24–27].

The following recommendations apply for patients not previously treated with DAA. Recommendation grade A1 if not otherwise stated.

Genotype 1

Non-cirrhosis – fibrosis stage F0–F3

One of the following treatment options is recommended:

- Glecaprevir/pibrentasvir 8 weeks [28,29].
- Grazoprevir/elbasvir 12 weeks for genotype 1b. For genotype 1a and low viral load (<800,000 IU/mL) 12 weeks without ribavirin. For genotype 1a and high viral load (>800,000 IU/mL) 16 weeks duration in combination with ribavirin is recommended. If susceptibility testing has been performed and baseline NS5A RASs/RAVs is not detected, 12 weeks without ribavirin, irrespective of viral load [23,30,31].
- Ombitasvir/paritaprevir/ritonavir + dasabuvir: For genotype 1b 8 weeks for prior untreated patients with fibrosis stage ≤ F2, but for F3 or prior interferon/ribavirin treated patients 12 weeks is recommended. For genotype 1a 12 weeks in combination with ribavirin [32–34].
- Sofosbuvir + daclatasvir 12 weeks [35].
- Sofosbuvir/ledipasvir 12 weeks [36–40]. Treatment for 8 weeks is efficacious for most patients without cirrhosis [40].
- Sofosbuvir + simeprevir 12 weeks [41,42].
- Sofosbuvir/velpatasvir 12 weeks [43].

Sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is approved for genotype 1, but had lower efficacy than sofosbuvir/velpatasvir for 12 weeks [44,45], and is therefore not recommended. This triple combination should for now primarily be used for retreatment of patients having relapsed after DAA therapy [46].

Compensated cirrhosis – fibrosis stage F4

- Glecaprevir/pibrentasvir 12 weeks [47].
- Grazoprevir/elbasvir 12 weeks for genotype 1b. For genotype 1a and low viral load (<800,000 IU/mL) 12 weeks without ribavirin. For genotype 1a and high viral load (>800,000 IU/mL) 16 weeks duration in combination with ribavirin is recommended. If susceptibility testing has been performed and baseline NS5A
RASs/RAVs is not detected, 12 weeks without ribavirin, irrespective of viral load [23,30,31].

- **Ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin** for 12 weeks for genotype 1b [48], and 24 weeks for genotype 1a [49,50]. Ribavirin should be added for genotype 1a, but not for genotype 1b.
- **Sofosbuvir + daclatasvir + ribavirin** 12 weeks or 24 weeks without ribavirin (recommendation grade B1).
- **Sofosbuvir/ledipasvir + ribavirin** 12 weeks [51,52]. Treatment without ribavirin for 12 weeks can be given to treatment-naive patients.
- **Sofosbuvir/velpatasvir** 12 weeks [43].
  - Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is approved for genotype 1, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].
  - Sofosbuvir + simeprevir + ribavirin for 12 weeks, or 24 weeks without ribavirin, is available, but is not primarily recommended because of impaired efficacy in the presence of baseline resistance to protease inhibitors [53].

**Genotype 2**

**Non-cirrhosis – fibrosis stage F0-F3**

- **Glecaprevir/pibrentasvir** 8 weeks [28,29].
- **Sofosbuvir/velpatasvir** 12 weeks [43,54].
  - Sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

**Compensated cirrhosis – fibrosis stage F4**

- **Glecaprevir/pibrentasvir** 12 weeks (16 weeks may be considered for patients having relapsed after interferon-based therapy (recommendation grade B2)) [56].
- **Sofosbuvir/velpatasvir** 12 weeks.
- **Sofosbuvir + daclatasvir +/− ribavirin** 24 weeks (recommendation grade B1), 16 weeks with ribavirin can be considered.
  - Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

**Genotype 3**

**Non-cirrhosis – fibrosis stage F0-F3**

- **Glecaprevir/pibrentasvir** 8 weeks (16 weeks may be considered for patients having relapsed after interferon-based therapy (recommendation grade B2)).
- **Sofosbuvir + daclatasvir** 12 weeks [55].
- **Sofosbuvir/velpatasvir** 12 weeks [43,54].
  - Sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

**Compensated cirrhosis – fibrosis stage F4**

- **Glecaprevir/pibrentasvir** 12 weeks [28,29].
- **Grazoprevir/elbasvir** 12 weeks [23]. Addition of ribavirin and 16 weeks should be considered if viral load >800,000 IU/mL (recommendation grade B2).
- **Ombitasvir/paritaprevir/ritonavir + ribavirin** 12 weeks [57].
- **Sofosbuvir + daclatasvir** 12 weeks (recommendation grade B1).
- **Sofosbuvir/ledipasvir** 12 weeks [58,59].
- **Sofosbuvir + simeprevir** 12 weeks (recommendation grade B1).
- **Sofosbuvir/velpatasvir** 12 weeks [43].
  - Sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

**Genotype 4**

**Non-cirrhosis – fibrosis stage F0–F3**

- **Glecaprevir/pibrentasvir** 8 weeks [28,29].
- **Grazoprevir/elbasvir** 12 weeks [23]. Addition of ribavirin and 16 weeks should be considered if viral load >800,000 IU/mL (recommendation grade B2).
- **Ombitasvir/paritaprevir/ritonavir + ribavirin** 12 weeks [57].
- **Sofosbuvir + daclatasvir** 12 weeks (recommendation grade B1).
- **Sofosbuvir/ledipasvir** 12 weeks [58,59].
- **Sofosbuvir + simeprevir** 12 weeks (recommendation grade B1).
- **Sofosbuvir/velpatasvir** 12 weeks [43].
  - Sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

**Compensated cirrhosis – fibrosis stage F4**

- **Glecaprevir/pibrentasvir** 12 weeks (recommendation grade A2).
- **Grazoprevir/elbasvir** 12 weeks [23]. Addition of ribavirin and 16 weeks should be considered if viral load >800,000 IU/mL (recommendation grade B2).
- Ombitasvir/paritaprevir/ritonavir + ribavirin 12 weeks.
- Sofosbuvir + daclatasvir + ribavirin 12 weeks, or 24 weeks without ribavirin.
- Sofosbuvir/ledipasvir + ribavirin 12 weeks, or 24 weeks without ribavirin.
- Sofosbuvir + simeprevir + ribavirin 12 weeks, or 24 weeks without ribavirin.
- Sofosbuvir/velpatasvir 12 weeks.
  Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

Genotype 5 and 6

Non-cirrhosis – fibrosis stage F0–F3
- Glecaprevir/pibrentasvir 8 weeks [28,29].
- Sofosbuvir/ledipasvir 12 weeks [60,61] (recommendation grade B1).
- Sofosbuvir/velpatasvir 12 weeks [43] (recommendation grade B1).
  Sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

Compensated cirrhosis – fibrosis stage F4
- Glecaprevir/pibrentasvir 12 weeks
- Sofosbuvir/ledipasvir +/- ribavirin 12 weeks (recommendation grade B2).
- Sofosbuvir/velpatasvir 12 weeks (recommendation grade B1).
  Sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is approved, but it is the opinion of the consensus group that this triple combination should primarily be used for retreatment of patients having relapsed after DAA therapy [46].

Treatment of patients with decompensated liver cirrhosis

These patients should be treated in collaboration with an experienced hepatologist, and treated in the same manner whether or not they are on the transplant waiting list. These patients should be monitored more closely during therapy than those with compensated liver disease. The choice of treatment selection should be based on HCV genotype. Patients with a short life expectancy and who are not candidates for liver transplantation are unlikely to benefit from antiviral therapy. Patients with hepatocellular carcinoma (HCC) and ongoing HCV infection should be treated in the same manner as those without HCC. If a patient with HCC is on the waiting list for liver transplantation, antiviral therapy can be deferred until after the transplantation if the expected waiting period is short. Treatment regimens containing protease inhibitors are not recommended for Child-Pugh B cirrhosis, and contraindicated in Child-Pugh C. Retreatment options are thus limited in these patients, and therefore, prolonged initial treatment duration may be considered. For ribavirin intolerant patients, 24 weeks of therapy is recommended (recommendation grade B2).

Genotype 1 or 4
- Sofosbuvir/ledipasvir + ribavirin 12 weeks.
- Sofosbuvir + daclatasvir + ribavirin 12 weeks (recommendation grade B1).
- Sofosbuvir/velpatasvir + ribavirin 12 weeks (has only been studied for Child-Pugh B) (recommendation grade B1) [62].

Genotype 2
- Sofosbuvir + daclatasvir + ribavirin 12 weeks (recommendation grade B2).
- Sofosbuvir/velpatasvir + ribavirin 12 weeks (has only been studied for Child-Pugh B) (recommendation grade B1) [62].

Genotype 3
- Sofosbuvir/velpatasvir + ribavirin 12 weeks (has only been studied for Child-Pugh B) (recommendation grade B1) [62].
- Sofosbuvir + daclatasvir +/- ribavirin 24 weeks (recommendation grade B1).
  Thus, the addition of ribavirin is recommended in all regimens for patients with decompensated cirrhosis, in spite of poorer tolerance. In the ASTRAL-4 study [62], which is the basis of the recommendation for sofosbuvir/velpatasvir, weight-based dosing of ribavirin was given, and doses were lowered if necessary. If standard dosing of ribavirin is used at the initiation of therapy, rapid dose reductions should be performed in the event of anaemia. Alternatively, a starting daily dose of 600 mg can be considered, which if tolerated, may be increased to the normal weight-
based dosing (1000 or 1200 mg). With lower dosing the risk of relapse unfortunately increases, especially among obese patients.

Pharmacokinetic drug–drug interactions during treatment with direct-acting antivirals

The risk of interactions differs considerably between DAAs. This applies to their impact on the exposure to other drugs, as well as the effect on their own pharmacokinetic profile. Thus prior to therapy, careful review of the patient’s current medication should be undertaken, including assessment of nonprescription medicines, dietary supplements as well as health care products. If the most appropriate DAA combination from an interaction perspective requires dose adjustments, changes in or temporary discontinuation of the patient’s current medication should be considered first prior to changes in the antiviral regimen. Only if this is not possible, should changes in the recommend DAA dosing be considered.

Contraindications and side effects

Contraindications regarding direct-acting antivirals

Contraindications are few, and vary slightly between DAAs. Pregnancy should be avoided with all HCV treatment regimens, as experience of treatment during pregnancy is limited.

Contraindications to ribavirin

Pregnancy, breastfeeding or a history of or on-going heart disease.

Side-effects of direct-acting antivirals

Side-effect profiles vary between DAAs, but those reported thus far are few and mostly mild. In general, the proportion of pre-mature termination of therapy secondary to adverse events has been very low in clinical trials (<1%), often compatible with placebo.

Side-effects of ribavirin

The major side-effect of ribavirin is haemolytic anaemia, with a mean decrease in haemoglobin of about 20 g/L during treatment. Additionally, ribavirin can cause itching and rash. Cough and neuropsychiatric side-effects, such as insomnia, are less frequent. Approximately a third of individuals have genetic variants of the inosine triphosphate pyrophosphatase (ITPA) gene entailing reduced enzymatic activity, and among these patients the risk of ribavirin-induced anaemia is reduced and therapeutic efficacy of ribavirin improved [21].

Monitoring during treatment

- HCV RNA quantification (the limit of detection should be ≤10–15 IU/ml): At start of therapy, week 4, at end-of-treatment (alternatively a sample may be frozen for later evaluation in the event of relapse), and at 1–2 occasions ≥12 weeks after end-of-treatment. If clinically motivated, closer monitoring of HCV RNA should be performed.
- If co-infection with chronic hepatitis B virus (HBV) infection, HBV DNA should be monitored during HCV therapy because of the risk of reactivation.
- Haemoglobin (if ribavirin is given) and ALT: weeks 2 and 4, and thereafter every fourth week. Cirrhotic patients should be monitored more frequently. Monitoring can be performed by a trained nurse who, under the supervision of a physician, informs the patients of the results of analyses and registers adverse events. Adherence is crucial in order to achieve a favourable therapeutic outcome, and therefore should be discussed at each visit. For patients with detectable HCV RNA after 4 weeks of antiviral therapy, adherence should be discussed.

Management of ribavirin-induced anaemia

The dose of ribavirin should be reduced at haemoglobin concentrations below 100 g/L, and should temporarily discontinued at levels below 85 g/L. Reduction of ribavirin has not been associated with reduced efficacy of DAA treatment.

Follow-up

HCV RNA in plasma should be analyzed when discontinuing treatment (alternatively a sample may be frozen for later evaluation in the event of relapse), and ≥12 weeks after termination of treatment. The positive predictive value of SVR12 for SVR24 is >99%, and therefore undetectable HCV RNA at a sampling at least 3 months after termination of treatment may be considered as equivalent to cure. A second undetectable HCV RNA plasma sample ≥12 weeks after termination of treatment may be advisable to avoid potential sample mishandling or other mishaps in the analysis process.
In spite of achieving SVR, patients will continue to have antibodies directed against HCV, and thus may not donate blood. However, organs from anti-HCV-positive donors may be accepted. Patients achieving SVR should be advised that they are not immune to the re-infection with HCV.

The annual risk of developing HCC is reduced from approximately 3–4% to 1% after achieving SVR in patients with compensated cirrhosis [4,6]. Until more data are generated, continued surveillance with a biannual liver ultrasound investigation, and possible evaluation of α-fetoprotein, is recommended in patients with cirrhosis because of the residual risk of HCC (recommendation grade B1).

Patients undergoing HCV treatment or follow-up after therapy should be reported in the national quality registry for hepatitis.

Re-treatment of patients who have failed direct-acting antiviral treatment

During unsuccessful DAA therapy, selection of RASs/RAVs with reduced susceptibility to one or more drugs occurs commonly. Sofosbuvir, however, appears to be an exception as NSSB RASs/RAVs only transiently have been observed in isolated cases. Sofosbuvir is thus the only DAA documented to retain full effect upon re-treatment.

Selected NS3/4A RASs/RAVs tend to revert back to fully sensitive wild-type virus over a period of 1-3 years. Although still not formally studied, NS3/4A protease inhibitors likely may be re-used in subsequent re-treatment regimens, provided sufficient time has passed to allow for reversion to wild-type virus.

In contrast, reversion appears less likely if selection of NSSA RASs/RAVs occurs, as these variants seem more persistent. However, NSSA inhibitors might retain partial activity even in the presence of resistant variants, and may thus possibly contribute to re-treatment.

DAA therapy is very efficacious, but irrespective of therapeutic regimen, a small group will continue to have detectable HCV RNA after therapy (i.e. non-SVR). Such patients should be retreated in collaboration with an experienced expert. The availability of combinations containing three antivirals with differing modes of action, however, has simplified retreatment.

The following triple therapy options are currently available:

- Sofosbuvir/velpatasvir/voxilaprevir
- Sofosbuvir + grazoprevir/elbasvir
- Sofosbuvir + glecaprevir/pibrentasvir

Of the abovementioned combinations, currently, only 12 weeks of sofosbuvir/velpatasvir/voxilaprevir is approved within the European Union. The remaining combinations potentially have good efficacy, but documentation is limited.

The addition of ribavirin is not mandatory, but may be considered, especially in patients previously treated with an NS5A-inhibitor or infected with HCV genotype 3 infection. Susceptibility testing for RASs/RAVs is not necessary prior to retreatment. Resistance against previously used antiviral agents presumably is present, but does not appear to impair the efficacy of triple DAA retreatment therapy. However, if SVR is not achieved in spite of an additional second DAA course irrespective of regimen, a thorough evaluation is required, including susceptibility testing. Poor adherence should also be excluded.

Relapsing patients with decompensated cirrhosis, where protease inhibitors should not be given, should receive 24 weeks of therapy including sofosbuvir, an NS5A-inhibitor, and ribavirin. Susceptibility testing for RASs/RAVs should be performed before the first attempted retreatment in these cases.

Treatment of patients accepted for liver transplant

These patients should be managed in collaboration with a liver specialist affiliated with a transplant centre, and there is often an immediate indication for therapy. If renal and hepatic function permits, patients with HCV infection who are on the waiting list for liver transplantation may receive antiviral treatment.

These patients can be divided into two groups: (i) patients with compensated cirrhosis and HCC, where the tumour is the main indication for liver transplantation, and (ii) patients with decompensated cirrhosis, where severe hepatic impairment motivates transplantation. If HCV treatment needs to be continued after transplantation, paritaprevir/ritonavir-based treatment should be avoided due to the risk of drug interactions with immunosuppressive drugs. If cyclosporine use is planned, potential drug–drug interactions should be thoroughly evaluated.

In 2016, a study from Spain reported an unexpected high rate of early tumour recurrence in 58 patients with HCV-related HCC undergoing interferon-free therapy [63]. Other studies [64], including a meta-analysis of 41 studies including 13,875 patients [65], have failed to find an effect of DAA therapy on the recurrence of hepatocellular carcinoma.
Recommendation for sampling while on the waiting list

During HCV therapy

- HCV RNA quantification should be analyzed at the start of therapy, and henceforth once weekly until the week after the first sample with undetectable HCV RNA.
- Thereafter, HCV RNA quantification should be performed every fourth week until the transplantation.

After completion of HCV treatment

- HCV RNA quantification should be assessed at 2 and 4 weeks post treatment.
- Thereafter, HCV RNA quantification every fourth week until the transplantation has been performed or SVR12 has been achieved in the event of a prolonged waiting period.

In the event of relapse after treatment while on the waiting list, possible re-treatment before liver transplantation should be discussed with a specialist at the transplant centre. An alternative approach is to postpone re-treatment until the first appropriate time-point after transplantation.

Information regarding HCV RNA levels must be continuously reported to the transplant clinic, as this impacts on whether the HCV treatment should continue to be administered in the peri- and postoperative phase.

Considerations at the time of transplantation

If the patient has been virus-free for \( \geq 4 \) weeks before transplantation:

Discontinue treatment when the transplantation is performed even if the full intended treatment duration has not been given (recommendation grade B1).

If the patient has been virus-free <\( 4 \) weeks before transplantation:

Continue treatment, without interruption, for 8–12 weeks after transplantation (recommendation grade B1). Consider discontinuing or reducing ribavirin dosing if renal impairment occurs post-transplant.

Treatment after liver transplantation

All patients who are viraemic at the time of transplantation will relapse upon reperfusion of the transplanted liver. Furthermore, HCV-associated liver disease progresses more rapidly in liver transplant recipients than in non-transplanted patients. Thus, HCV-infected transplant recipients should be offered treatment regardless of fibrosis stage at the earliest appropriate time-point after transplantation.

The choice of therapy follows the same principles as in non-transplanted patients, taking into account HCV genotype, fibrosis stage, and renal function. Because of potential drug interactions, regimens including paritaprevir/ritonavir should not be used. If cyclosporine is included in the immunosuppressive regimen, simeprevir concentrations likely will increase, and thus will require monitoring. If, prior to transplantation, the patient has relapsed despite a full DAA treatment course, this should be considered before initiation of re-treatment.

Secondary to potential drug interactions and expected improvements in liver function, including increased metabolism, close monitoring of immunosuppressive drug concentrations at initiation as well as discontinuation of antiviral therapy is recommended (Table 2).

Treatment before or after other solid organ, stem cell transplantation, or other immunosuppressive therapy

Patients undergoing evaluation for transplantation of organs other than the liver or other immunosuppressive therapy should be treated before the initiation of immunosuppression, if possible.

Potential drug interaction with immunosuppressive medication used in recipients of organ transplantations other than the liver should be handled as described above.

Treatment of patients with renal insufficiency

DAA use in patients with renal impairment

For patients with mild to moderate renal impairment (glomerular filtration rate (GFR) \( \geq 30 \) mL/minute), the same treatment options apply as for patients with normal renal function.

The following treatment alternatives can be given regardless of renal function (including haemodialysis patients), and either of the following treatment options, at the same dose as in patients with normal renal function, is primarily recommended if GFR <\( 30 \) mL/minute:

- Glecaprevir/pibrentasvir for all genotypes [66].
- Grazoprevir/elbasvir for genotype 1 or 4 (without the addition of ribavirin as in the registration trial) [67].

Ombitasvir/paritaprevir/ritonavir ± dasabuvir for genotypes 1 and 4 is also approved for this indication, but is
not recommended as it is more complex than the abovementioned alternatives and requires the addition of ribavirin for genotype 1a or 4 [68].

Currently, there is limited experience of sofosbuvir in patients with severe renal impairment (creatinine clearance <30 mL/min) or haemodialysis [69]. Exposure to the virologic inactive major metabolite of sofosbuvir (GS331007) increases with decreasing renal function. Despite this, sofosbuvir dosing does not need adjustment in the presence of mild to moderate renal impairment.

If an appropriate sofosbuvir-free regimen is not suitable, treatment should only be given if urgently needed. Sofosbuvir treatment of patients with renal impairment should only be given with careful monitoring and in close consultation with a nephrologist.

**Ribavirin use in renal impairment**

Ribavirin should be avoided in patients with reduced renal function, but if this is not possible, dosing should be given as suggested in Table 3 for an individual weighing 70 kg [70]. At steady state, which occurs after more than four weeks in patients with normal renal function treated with weight-based ribavirin dosing, i.e. 1000 or 1200 mg daily, trough ribavirin concentrations of approximately 8–12 μmol/L (2000–3000 ng/mL) generally are achieved [71]. In subjects with renal impairment the half-life of ribavirin is prolonged, and thus also the time before achieving steady state, which in severe renal impairment may take several months. Aside from renal function, plasma concentrations of ribavirin are also dependent on host genetic variants of *ITPA* [21].

**Treatment of patients co-infected with HCV and HIV**

Complications of chronic HCV infection are a major cause of morbidity and mortality in HIV-infected patients. In Sweden, approximately 10% of HIV-infected patients have antibodies against HCV.

The same recommendations regarding the indications for and contraindications to HCV treatment apply as for HCV mono-infected patients.

Studies on co-infected patients are still limited regarding number and sample size for many regimens. The SVR rates observed in studies using modern regimens, however, are similar to those achieved in HCV mono-infected patients [72–74].

The most important factor to consider when treating co-infected patients is the potential risk of drug–drug interactions between HIV and HCV treatment regimens. For patients receiving a complex HIV treatment, it may be difficult to evaluate possible interactions, and in such cases, contact with a specialist in the field is recommended. If the on-going HIV treatment needs modification, this should be performed prior to the initiation of the HCV treatment.

Patients with on-going HIV treatment should have stable virological control of their HIV infection prior to initiating HCV treatment. CD4 T cell levels are not considered a significant predictor of the likelihood of achieving SVR [72–74].

In the event of a newly diagnosed HIV infection, treatment of the HIV infection should be prioritized before HCV therapy.

The same recommendations regarding sampling apply as for patients with HCV mono-infection, and HIV monitoring may follow normal clinical routines.

---

**Table 2.** Interactions between DAAs and calcineurin inhibitors.

| DAA                              | Ciclosporin                        | Tacrolimus                       |
|----------------------------------|------------------------------------|----------------------------------|
| Sofosbuvir                       | No dose adjustment required        | No dose adjustment required      |
| Simeprevir                       | Not recommended                    | Not recommended                  |
| Sofosbuvir/ledipasvir             | No dose adjustment required        | No dose adjustment required      |
| Sofosbuvir/velpatisvir           | No dose adjustment required        | No dose adjustment required      |
| Sofosbuvir/velpatisvir/voxilaprev| Not recommended                    | The dose must be adjusted considerably. |
| Ombitasvir/panitaprevir/ritonavir| The dose must be adjusted considerably. | Not recommended                  |
| Dasabuvir                        | The dose must be adjusted considerably. | Not recommended                  |
| Grazoprevir/elbasvir             | Contraindicated                    | Close concentration monitoring required |
| Glecaprevir/pibrentasvir         | Not recommended if ciclosporin dose >100 mg/day | Use with caution; leads to increased tacrolimus concentrations |

**Table 3.** Suggested starting dose of ribavirin for patients weighing 70 kg with renal insufficiency adjusted according to creatinine clearance.

| Creatinine clearance (mL/min) | Starting dose of ribavirin (mg/day) |
|-------------------------------|------------------------------------|
| 80                            | 800                                |
| 60                            | 600                                |
| 40                            | 400                                |
| 20                            | 200                                |
Patients with ongoing or recently concluded substance abuse

Ongoing or recently concluded substance abuse is not a contraindication for HCV therapy. Instead, focus should be placed on individually assessing adherence to HCV treatment.

Treatment of PWIDs is likely a prerequisite to impact on the prevalence of HCV infection, and is required for future elimination of the disease. An elimination program would necessitate simultaneous and widespread treatment of such cohorts sharing similar risk behaviour (injection needles and paraphernalia). Patients with injection drug use may experience problems with compliance. In order to create optimal conditions for adherence to HCV therapy, a multidisciplinary approach is required. Thus, close contact with addiction and mental health expertise, as well as social services may be needed prior to initiating anti-viral therapy.

Studies have reported comparable therapeutic outcome among PWIDs and patients on opiate substitution therapy with methadone or buprenorphine [75–77]. Also in this setting, focus should be placed on a multidisciplinary approach in order to optimize adherence.

PWIDs achieving SVR should be offered appropriate supportive measures to prevent re-infection. The best protection against re-infection is achieved through a combination of participation in needle exchange programs and opiate substitution therapy, whereas needle exchange programs alone have limited effect. The potential risk of spread of resistant virus after failed DAA therapy among PWIDs should be considered, which further stresses the importance of harm reduction measures.

Advanced alcohol abuse, in addition to host genetic factors [78–81], also is a risk factor for deterioration of liver disease. Therefore, in order to reduce disease progression, the patient should be offered help to reduce or abolish alcohol intake. If a patient cannot abstain from alcohol, the initiation of HCV therapy should be based on the likelihood of adhering to treatment.

Children and adolescents (<18 years) with chronic HCV infection

The prevalence of chronic HCV infection is less than 0.5% among European children [82]. During the past decade, approximately 100 such cases have been reported annually to the Swedish Public Health Agency, with half being below 16 years of age. In light of the expected annual number of infections secondary to mother-child transmission [83] as well as the number of children immigrating to Sweden from countries with higher HCV prevalence, this number may be an underestimate of the true incidence.

The risk of developing a chronic infection in children appears to be equivalent (55–80%) to that seen in adults. Spontaneous resolution of infection after vertical transmission may occasionally occur until the age of five, and is reportedly related to the host IL28B (also known as IFNL4) genotype [84]. Among those developing a chronic HCV infection, progression of liver fibrosis may occur, and approximately 2–3% of teenagers infected early in life develop cirrhosis, some requiring liver transplantation.

Evaluation and treatment decisions during childhood

In children with chronic HCV infection, the same sampling and monitoring as for adults should be performed. The interpretation of serological analyses in children born to infected mothers is complicated by the presence of residual maternal antibodies for up to 15 months of age. Serological screening at 18 months of age is recommended for children born to HCV-infected mothers, and in case of positive antibody reactivity in the screening test, infection must be confirmed by HCV RNA analysis. Children with confirmed chronic HCV infection should be monitored annually by liver function tests and every 2–3 years with HCV RNA quantification. The need for antiviral therapy should be evaluated in collaboration with a specialist experienced with HCV treatment in paediatric patients.

Thus far, there are two published reports on the use of DAA therapy among HCV genotype-infected adolescents aged 12 to 17 years, sofosbuvir/ledipasvir for genotype 1 [85] and sofosbuvir + ribavirin for genotypes 2 or 3 infection [86]. In the first study 98 of 100 (98%) achieved SVR, and in the latter, 51 of 52 (98%). In both of these studies adult dosing was used, and the adverse event profile was similar to that reported in adults. Both of these regimens are now approved by the FDA and EMA for use in children aged 12–17 years. For other DAA regimens and in younger children (age 6–11 years), studies are ongoing. It is important to treat chronically infected children and adolescents, because of the long expected duration of infection as well as the reduced risk of transmission after successful therapy.

Fibrosis stage in children can be assessed by liver biopsy or elastography using an appropriate child probe. The relationship between histological fibrosis stage and elastography is less well documented in children.
However, similar cut-off levels as for adults may probably be used.

**Choice of treatment for children with chronic HCV**

Treatment can be given from 12 years of age using:

- sofosbuvir/ledipasvir 12 weeks for genotype 1 or 4.
- sofosbuvir + ribavirin 12–24 weeks for genotypes 2 or 3.

For genotypes 2 or 3, sofosbuvir/velpatasvir 12 weeks may be an alternative from 12 years of age although this is not yet formally approved.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**ORCID**

Martin Lagging http://orcid.org/0000-0002-7995-3626
Ann-Sofi Duberg http://orcid.org/0000-0001-7248-0910
Soo Aleman http://orcid.org/0000-0003-0461-4870
Ola Weiland http://orcid.org/0000-0002-6934-9724
Johan Westin http://orcid.org/0000-0003-1033-1826

**References**

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

[2] Seeff LB. The history of the “natural history” of hepatitis C (1968 – 2009). Liver Int. 2009;29(Suppl 1):89–99.

[3] Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34:809–816.

[4] Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology. 2004;127(Suppl 1):535–550.

[5] Lagging M, Wejstal R, Norkrans G, et al. Treatment of hepatitis C virus infection: updated Swedish guidelines 2016. Infect Dis (Lond). 2017;49:561–575.

[6] Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis. 2013;57:230–236.

[7] Batts KP, Ludwig J. Chronic hepatitis: An update on terminology and reporting. Am J Surg Pathol. 1995;19:1409–1417.

[8] Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAIRV Cooperative Study Group. Hepatology. 1996;24:289–293.

[9] European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. J Hepatol. 2015;63:199–236.

[10] Hansen JF, Juul Nielsen M, Nystrom K, et al. PRO-C3: a new and more precise collagen marker for liver fibrosis in patients with chronic hepatitis C. Scand J Gastroenterol. 2018;53:83–87.

[11] Andreasson K, Waldenstrom J, Westin J, et al. Cartilage oligomeric matrix protein associates with hepatic inflammation and fibrosis in hepatitis C virus infection. J Hepatol. 2017;67:649–651.

[12] Ydreborg M, Lisovskaia V, Lagging M, et al. A novel fibrosis index comprising a non-cholesterol sterol accurately predicts HCV-related liver cirrhosis. PLoS One. 2014;9:e93601.

[13] Westin J, Ydreborg M, Islam S, et al. A non-invasive fibrosis score predicts treatment outcome in chronic hepatitis C virus infection. Scand J Gastroenterol. 2008;43:73–80.

[14] Islam S, Antonsson L, Westin J, et al. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scand J Gastroenterol. 2005;40:867–872.

[15] Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology. 2012;142:1293–1302 e4.

[16] Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology. 2009;49:1821–1827.

[17] de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015;63:743–752.

[18] Guidelines for the screening care and treatment of persons with chronic Hepatitis C infection: updated version. Geneva: WHO Guidelines Approved by the Guidelines Review Committee; 2016.

[19] Rembeck K, Lagging M. Impact of IL28B, ITPA and PNPLA3 genetic variants on therapeutic outcome and progression of hepatitis C virus infection. Pharmacogenomics. 2015;16:1179–1188.

[20] Waldenstrom J, Nystrom K, Lagging M. Do variations in the ITPA gene determine the risk of hepatitis C virus relapse? Future Microbiol. 2014;9:1009–1012.

[21] Rembeck K, Waldenstrom J, Hellstrand K, et al. Variants of the inosine triphosphate pyrophosphatase gene are associated with reduced relapse risk following treatment for HCV genotype 2/3. Hepatology. 2014;59:2131–2139.

[22] Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. J Hepatol. 2016;64:486–504.

[23] Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and non-cirrhotic patients with chronic Hepatitis C Virus Genotype 1, 4, or 6 infection. Ann Intern Med. 2015;163:1–13.

[24] Waldenstrom J, Farkkila M, Rembeck K, et al. Short interferon and ribavirin treatment for HCV genotype 2 or 3 infection: NORDynamIC trial and real-life experience. Scand J Gastroenterol. 2016;51:337–343.

[25] Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008;47:1837–1845.
[26] Lagging M, Afdhal N, Pedersen C, et al. Weight-adjusted dosing of ribavirin and importance of hepatitis C virus RNA below 1000 IU/mL by day 7 in short-term peginterferon therapy for chronic genotype 2/3 hepatitis C virus infection. Hepatology. 2008;48:695.

[27] Lagging M, Alsio S, Hellstrand K, et al. Is HCV RNA analysis at day 7 cost-effective in deciding the duration of therapy in chronic HCV genotype 2/3 infection? J Hepatol. 2011;54:835–836. author reply 836-837.

[28] Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with Hepatitis C Virus Genotype 2, 4, 5, or 6 infection without cirrhosis. Clin Gastroenterol Hepatol. 2018;16:417–426.

[29] Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J Hepatol. 2017;67:263–271.

[30] Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385:1075–1086.

[31] Lagging M, Brown A, Mantry PS, et al. Grazoprevir plus peginterferon and ribavirin in treatment-naive patients with hepatitis C virus genotype 1 infection: a randomized trial. J Viral Hepat. 2016;23:80–88.

[32] Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1594–1603.

[33] Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370:1983–1992.

[34] Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1604–1614.

[35] Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med. 2014;370:211–221.

[36] Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014;383:515–523.

[37] Mizokami M, Yokosuka O, Takehara T, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with hepatitis 1C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015;15:645–653.

[38] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889–1898.

[39] Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370:1483–1493.

[40] Kowdle KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370:1879–1888.

[41] Lawitz E, Sulkowski MS, Ghalb R, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014;384:1756–1765.

[42] Kwo P, Gitlin N, Nahass R, et al. Simeprevir plus sofosbuvir (12 and 8 weeks) in hepatitis C virus genotype 1-infected patients without cirrhosis: OPTIMIST-1, a phase 3, randomized study. Hepatology. 2016;64:370–380.

[43] Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373:2599–2607.

[44] O’Brien TR, Kottill S, Pfeiffer RM. IFNL4 genotype is associated with virologic relapse after 8-week treatment with sofosbuvir, velpatasvir, and voxilaprevir. Gastroenterology. 2017;153:1694–1695.

[45] Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology. 2017;153:113–122.

[46] Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med. 2017;376:2134–2146.

[47] Forns X, Lee SS, Valdes J, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. Lancet Infect Dis. 2017;17:1062–1068.

[48] Kumada H, Chayama K, Rodrigues L, Jr, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology. 2015;62:1037–1046.

[49] Lawitz E, Makara M, Akarca US, et al. Efficacy and safety of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology. 2015;62:1037–1046.

[50] Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370:1973–1982.

[51] Bourliere M, Bronowicki JP, de Ledinghen V, et al. Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS). Lancet Infect Dis. 2015;15:397–404.

[52] Reddy KR, Bourliere M, Sulkowski M, et al. Ledipasvir and sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: an integrated safety and efficacy analysis. Hepatology. 2015;62:79–86.

[53] Lawitz E, Matusow G, DeJesus E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: a phase 3 study (OPTIMIST-2). Hepatology. 2016;64:360–369.
[54] Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV Genotype 2 and 3 infection. N Engl J Med. 2015;373:2608–2617.

[55] Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61:1127–1135.

[56] Wyles D, Poordad F, Wang S, et al. Glecaprevir/Pibrentasvir for HCV Genotype 3 patients with cirrhosis and/or prior treatment experience: a partially randomized phase III clinical trial. Hepatology. 2017 [Sep 19]. DOI: 10.1002/hep.29541

[57] Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015;385:2502–2509.

[58] Kohli A, Kapoor R, Sims Z, et al. Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study. Lancet Infect Dis. 2015;15:1049–1054.

[59] Smith MA, Mohammad RA. Ledipasvir-sofosbuvir for hepatitis C genotype 4 infection. Lancet Infect Dis. 2015;15:993–995.

[60] Abergel A, Loustaud-Ratti V, Metvivier A. Ledipasvir/sofosbuvir treatment results in high SVR rates in patients with chronic genotype 4 and 5 HCV infection. J Hepatol. 2015;62:S219.

[61] Gane EJ, Hyland RH, An D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV Genotype 3 or 6 infection. Gastroenterology. 2015;149:1454–1461.

[62] Curry MP, O’Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med. 2015;373:2618–2628.

[63] Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumour recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016;65:719–726.

[64] Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol. 2016;65:734–740.

[65] Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. J Hepatol. 2017;67:1204–1212.

[66] Gane E, Lawitz E, Pugatch D, et al. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med. 2017;377:1448–1455.

[67] Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386:1537–1545.

[68] Pockros PJ, Reddy KR, Mantry PS, et al. Safety of ombitasvir/paritaprevir/ritonavir plus dasabuvir for treating HCV gt1 infection in patients with severe renal impairment or end-stage renal disease: the RUBY-I study. J Hepatol. 2015;62:5257.

[69] Hundemer GL, Sise ME, Wisocky J, et al. Use of sofosbuvir-based direct-acting antiviral therapy for hepatitis C viral infection in patients with severe renal insufficiency. Infect Dis (Lond). 2015;47:924–929.

[70] Bruchfeld A, Lindahl K, Schwarz R, et al. Dosage of ribavirin in patients with hepatitis C should be based on renal function: a population pharmacokinetic analysis. Ther Drug Monit. 2002;24:701–708.

[71] Wyles DL, Ruane PJ, Sulkowski MS, et al. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373:705–713.

[72] Naggie S, Cooper C, Saag M, et al. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med. 2015;373:714–725.

[73] Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA. 2015;313:1223–1231.

[74] Dore GJ, Altice F, Litwin AH, et al. Elbasvir-grazoprevir to treat Hepatitis C virus infection in persons receiving opioid agonist therapy. Ann Intern Med. 2016;165:625–634.

[75] Puoti M, Panzeri C, Rossotti R, et al. Efficacy of sofosbuvir-based therapies in HIV/HCV infected patients and persons who inject drugs. Dig Liver Dis. 2014;46(Suppl 5):S206–S211.

[76] Lalezari J, Sullivan JG, Varunok P, et al. Ombitasvir/paritaprevir/ritonavir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol. 2015;63:364–369.

[77] Lagging M. Impact of IL28B SNPs on therapeutic outcome and liver histology differs between hepatitis C virus genotypes. Pharmacogenomics. 2012;13:847–849.

[78] Rembek K, Alsio A, Christensen PB, et al. Impact of IL28B-related single nucleotide polymorphisms on liver histopathology in chronic hepatitis C genotype 2 and 3. PLoS One. 2012;7:e29370.

[79] Rembek K, Maglio C, Lagging M, et al. PNPLA 3 I148M genetic variant associates with insulin resistance and baseline viral load in HCV genotype 2 but not in genotype 3 infection. BMC Med Genet. 2012;13:82.

[80] Ydreborg M, Westin J, Rembeck K, et al. Impact of IL28B-related single nucleotide polymorphisms on liver transient elastography in chronic hepatitis C infection. PLoS One. 2013;8:e80172.

[81] Dominguez A, Bruguera M, Vidal J, et al. Community-based seroepidemiological survey of HCV infection in Catalonia, Spain. J Med Virol. 2001;65:688–693.

[82] Thomas SL, Newell ML, Peckham CS, et al. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. Int J Epidemiol. 1998;27:108–117.
[84] Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA, et al. Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. Hepatology. 2011;53:1830–1838.

[85] Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology. 2017;66:371–378.

[86] Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology. 2017;66:1102–1110.