CONTINUING MEDICAL EDUCATION

Treatment Options in Hepatitis C

The Current State of the Art

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SUMMARY

Background: Among patients with chronic hepatitis C, 20–30% develop hepatic cirrhosis and its complications within 30 years. The antiviral treatment of hepatitis C, previously interferon-based, has recently become interferon-free, with resulting improvements in sustained virological response rates, safety, and tolerability and a shorter duration of treatment.

Methods: This review is based on relevant publications retrieved by a selective literature search, and particularly on studies and reviews concerning the course and treatment of hepatitis C.

Results: The available drugs for interferon-free antiviral treatment of hepatitis C include inhibitors of the RNA-dependent RNA polymerase, NS3/4A protease, and NS5A protein of the hepatitis C virus (HCV), and ribavirin. Typically, two specific inhibitors are given in combination; the usual duration of treatment is 12 weeks. The antiviral drugs differ in their genotypic antiviral effectiveness and resistance barriers. The appropriate drug(s) should be chosen in consideration of the patient's hepatic and renal function and potential drug interactions. These drugs are safe and well-tolerated and result in sustained virological response rates between 90% and 100%.

Conclusion: All patients with hepatitis C, whatever their disease stage, can derive a sustained eradication of HCV from a combination of drugs with direct antiviral activity. Viral eradication is associated with a better quality of life and with lower morbidity and mortality.

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More than 100 million persons worldwide are infected with the hepatitis C virus (HCV). The prevalence of HCV in Germany is estimated at 0.3–0.5% (e1, e2). It is transmitted parenterally. Transmission via the transfusion of whole blood and blood products has been minimized through the use of serological and molecular testing procedures. The risk of transmission of HCV now arises mainly from needle sharing among intravenous drug abusers, homosexual contacts between men, and, in countries with poor adherence to hygiene guidelines, iatrogenic transmission (e3).

Acute hepatitis C takes a chronic course in 50–70% of cases. Hepatic fibrosis progresses is dependent on the age of the patient at the time of infection. On average, 20–30% of patients develop cirrhosis within 30 years (e3, e4). The progression of fibrosis is modulated by cofactors such as the amount of alcohol consumed or viral coinfections (e.g., with HIV) (e3, e4). Patients with HCV-associated cirrhosis have a 3–6% incidence of hepatocellular carcinoma (e5).

The treatment of HCV has been revolutionized by the recent introduction of potent direct antiviral agents (DAA).

Interferon-free treatment now gives patients an excellent chance of long-lasting virus eradication, i.e., a sustained virological response (SVR) (e6).

Learning objectives

The goals of this article are to:

- give the reader knowledge of the genotypic antiviral effectiveness, safety, and tolerability of the available inhibitors of RNA-dependent RNA polymerase, NS3/4A protease, and the NS5A protein;
- explain the treatment schemes recommended for different patient populations;
- discuss the importance of hepatic and renal function and potential drug interactions for the choice of antiviral drugs.

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Prevalence

The prevalence of HCV in Germany is estimated at 0.3–0.5%.

Methods

For this review, we evaluated publications about the antiviral treatment of hepatitis C from the years 2003 (first publication on the effective use of a direct antiviral agent in humans [e7]) to 2016 that were retrieved by a selective search in PubMed, with special attention to phase 2 and 3 trials and reviews on the course and treatment of hepatitis C. We also considered all abstracts of presentations on this subject within this time period that were given at the meetings of the German (DGVS), European (EASL), and American (AASLD) specialty societies, as well as these societies' HCV treatment guidelines.

Sustained viral response: a patient-relevant endpoint

The molecular demonstration of the absence of HCV-RNA twelve weeks after the end of a course of antiviral treatment confirms the sustained eradication of the virus. The likelihood of a late recurrence is well under 1% (e8, e9), and most such events are actually not recurrences but reinfections (e10). The eradication of HCV does not generate protective immunity (e11).

A meta-analysis of 129 studies involving a total of 34 563 patients who had undergone interferon-based treatment revealed that a sustained virological response was associated with a 62% to 84% reduction of mortality, a 68% to 79% reduction of the risk of hepatocellular carcinoma (HCC), and a 90% reduction of the risk of needing liver transplantation (e12). As interferon-based treatment was contraindicated in patients with decompensated cirrhosis, these data are uninformative with respect to any potential clinical benefit, for these patients, of sustained viral eradication with direct antiviral agents (DAA). Initial studies have yielded clinical and laboratory evidence of improvement mainly for patients with a MELD ("model of end-stage liver disease") score below 16–18 points (1–3). In large-scale cohort studies, sustained viral eradication was associated both with lower liver-associated mortality and with substantially lower extrahepatic mortality (although no causal link was demonstrated) (e13). Sustained viral eradication eliminates the risk of individual transmission and is associated with a better quality of life (4, e14).

Because of the residual risk of HCC even after successful viral eradication, patients with hepatic cirrhosis (regardless of the possible regression of fibrosis) should undergo lifelong surveillance with hepatic

ultrasonography and alpha-fetoprotein measurement every six months, as recommended in the German guideline (5). Esophageal varices are very unlikely to arise once HCV has been eradicated, because viral eradication is associated with the regression of hepatic fibrosis and portal hypertension (as reflected in the hepatovenous portal pressure gradient [HVPG]) (e15).

HCV genotypes

The genetic variability of the hepatitis C virus is high. There are at least six different genotypes (HCV-1, 2, 3, and others) with multiple subtypes (e.g., HCV-1a, 1b and more). The precise diagnosis can be established either by direct sequencing or by a reverse hybridization assay. Infection with HCV genotype 3 is associated with more rapid progression of fibrosis than infection with other HCV genotypes (e16). There are conflicting data on associations of specific HCV genotypes with the incidence of hepatocellular carcinoma (e17, e18).

Antiviral drugs

The basis of current, interferon-free treatment is a combination of directly acting antiviral drugs (*Table 1*) with high antiviral efficacy, resistance barriers, and different sites of attack (*Figure*) (6, 7).

RNA-dependent RNA polymerase inhibitors are categorized as either nucleotide inhibitors (NI) or non-nucleoside inhibitors (NNI). NI are phosphorylated within cells by the activity of cellular kinases, bind as triphosphates to the active center of the HCV-specific NS5B polymerase, and abort the construction of the growing viral RNA chain. NNI cause allosteric inhibition of NS5B polymerase. The generic names of all HCV polymerase inhibitors end in "-buvir." Protease inhibitors are directed against HCV-NS3/4A serine protease (splitting of the HCV polyprotein); their generic names end in "-previr." The HCV-NS5A protein plays a role in HCV replication and the modulation of cellular functions. Various NS5A inhibitors have been developed; these have generic names ending in "-asvir." (6). Ribavirin, a drug whose antiviral mechanism of action is still incompletely understood, continues to play an important role in various antiviral drug regimens (e19).

The treatment of acute hepatitis C

In the multicenter German "Acute HCV IV" trial, six weeks of treatment with sofosbuvir/ledipasvir resulted in a sustained viral eradication rate of 100% in

HCV genotypes

The genetic variability of the hepatitis C virus is high. There are at least six different genotypes with multiple subtypes.

Antiviral drugs

The basis of current, interferon-free treatment is a combination of directly acting antiviral drugs with high antiviral efficacy, resistance barriers, and different sites of attack.

TABLE 1

Antiviral drugs for the treatment of hepatitis C (HCV)

Substance class	Drug	Daily dose	HCV- genotype activity (in vitro and as approved)
Nucleotide polymerase inhibitors	sofosbuvir	400 mg	1a, b; 2a, b; 3a; 4a; 5a; 6a Approval: 1 through 6
Non-nucleoside polymerase inhibitors	dasabuvir	2 × 250 mg	1a, b Approval: 1
NS3/4A protease inhibitors	simeprevir	150 mg	1a, b; 2; 4; 5; 6 Approval: 1, 4
	paritaprevir (ritonavir-boosted)* ¹	2 × 75 mg (2 × 50 mg ritonavir)	1a, b; 2a; 4a; 6a Approval: 1, 4
	grazoprevir* ²	100 mg	1a, b; 4 Approval: 1, 4
NS5A inhibitors	daclatasvir	60 mg* ⁵	1a, b; (2a); 3a; 4a; 5a; 6a Approval: 1, 3, 4
	ledipasvir* ³	90 mg	1a, b; 2a,b; 3a; 4a,d; 5a; 6a, e Approval: 1, 4
	ombitasvir* ¹	2 × 12.5 mg	1, (2a), 2b, (3a), 4a, 5a Approval: 1, 4
	velpatasvir* ⁴	100 mg	1a, b; 2a, b; 3a; 4a, d, r; 5a; 6a, e Approval: 1 through 6
	elbasvir* ²	50 mg	1a, b; 4 Approval: 1, 4

*¹ Co-formulation per tablet: 75 mg paritaprevir, 50 mg ritonavir (as a pharmacokinetic booster), 12.5 mg ombitasvir

*² Co-formulation per tablet: 100 mg grazoprevir, 50 mg elbasvir

*³ Co-formulation per tablet: 400 mg sofosbuvir, 90 mg ledipasvir

*⁴ Co-formulation per tablet: 400 mg sofosbuvir, 100 mg velpatasvir

*⁵ Modify to 30 mg for patients simultaneously taking a strong inhibitor of CYP3A4 or 90 mg for patients simultaneously taking a moderate inducer of CYP3A4.

patients acutely infected with HCV genotype 1 (8). It should be noted, however, that the combination of sofosbuvir and ledipasvir is available in Germany only in packages of 28 tablets, so that taking a single tablet per day for six weeks (i.e., 42 tablets total) is unreasonable in terms of drug economics. Until further data are available, patients with acute hepatitis C should be treated for eight weeks, analogously to the recommendations for previously untreated (non-cirrhotic) patients with acute hepatitis C. As the rate of HCV transmission to health care workers via needle stick injury is very low, no post-exposure prophylaxis is recommended in this situation (9).

Treatment options

For previously untreated patients with chronic hepatitis C

Various drug combinations have been approved for the treatment of HCV genotype 1 infection, including both fixed co-formulations (sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, paritaprevir/ombitasvir with dasabuvir, grazoprevir/elbasvir) and combinations in which the doses of the two agents can be freely chosen (sofosbuvir plus simeprevir, sofosbuvir plus daclatasvir) (Table 2) (10–17). All combinations result in sustained virological response rates above 95% in this patient population and are generally very well tolerated. The duration of treatment is twelve weeks but can be

Polymerase inhibitors

RNA-dependent RNA polymerase inhibitors are categorized as either nucleotide inhibitors (NI) or non-nucleoside inhibitors (NNI). The generic names of all HCV polymerase inhibitors end in “-buvir.”

The treatment of acute hepatitis C

Six weeks of treatment with sofosbuvir/ledipasvir yields a sustained viral eradication rate of 100% in patients acutely infected with HCV genotype 1.

FIGURE

The replication cycle of the hepatitis C virus, with points of attack of antiviral drugs

shortened to eight in the case of sofosbuvir/ledipasvir for a previously untreated, non-cirrhotic patient with an HCV-RNA viral load under 6 million IU/mL, or paritaprevir/ombitasvir/dasabuvir for a previously untreated, non-cirrhotic patient with an HCV genotype 1b infection (10, 18, e20).

The administration of ribavirin in addition to paritaprevir/ombitasvir/dasabuvir is recommended for the treatment of patients who are infected with HCV genotype 1a, but not for those infected with HCV geno-

type 1b (12, 13, 19). Only limited evidence is now available on the possible role of ribavirin as an addition to the freely combinable regimens.

The European approval for the treatment of patients with HCV-1a infection with grazoprevir/elbasvir contains the recommendation that treatment for 16 weeks, with ribavirin given in addition, should be considered for patients whose initial viral load exceeds 800 000 IU/mL, in order to lower the risk of treatment failure. Alternatively, the decision to modify the treatment in

The treatment of previously untreated patients

Both fixed co-formulations and combinations in which the doses of the agents can be freely chosen have been approved for the treatment of HCV genotype 1 infection. All yield sustained virological response rates > 95% and are well tolerated.

Ribavirin

Ribavirin in addition to paritaprevir/ombitasvir/dasabuvir is recommended for the treatment of patients who are infected with HCV genotype 1a. Limited evidence is available on its possible role in addition to freely combinable regimens.

this way can be based on testing for resistance-associated variants (RAVs) of the NS5A gene, which lower the activity of elbasvir by at least a factor of 5 (14).

The standard treatment of HCV genotype 2 infection is with sofosbuvir/ribavirin (20), and that of HCV genotype 3 infection is with sofosbuvir/daclatasvir, for twelve weeks in both cases (21). Effective drug combinations for the treatment of HCV genotype 4 infection include sofosbuvir/ledipasvir (e21), paritaprevir/ombitasvir (without dasabuvir, but with ribavirin) (22), grazoprevir/elbasvir (23), sofosbuvir/daclatasvir (e22), and sofosbuvir/simeprevir (e23) (Table 2).

The first approved pangenotypic drug combination is that of sofosbuvir with velpatasvir, which yields virus eradication rates of 97–100% in infections with HCV genotype 1, 2, 3, 4, 5, or 6 (24, 25).

Patients previously treated with (peg-)interferon/ribavirin

The sustained virological response rates obtainable with all of the approved drug regimens are essentially the same in non-cirrhotic patients infected with HCV genotype 1 regardless of whether they are treatment-naïve or have been previously treated with (peg-)interferon/ribavirin (10–17). Nonetheless, there is an important distinction between patients infected with HCV genotype 1 who have been previously treated with a (peg-)interferon/ribavirin in combination with, or without, a direct antiviral agent (usually a first-generation NS3/4A protease inhibitor, such as telaprevir or boceprevir). Patients previously treated with a triple combination of peginterferon, ribavirin, and an NS3/4A protease inhibitor can be treated anew with sofosbuvir/ledipasvir (26), sofosbuvir/velpatasvir (24), or sofosbuvir/daclatasvir (27) without any compromise of the likelihood of a sustained virological response.

It is unusual (<10–15%) for a non-cirrhotic patient with an HCV genotype 2 infection to fail to respond to treatment with (peg-)interferon/ribavirin. Retreatment options for such patients include sofosbuvir/ribavirin for 12–16 weeks (28) and sofosbuvir/velpatasvir for 12 weeks (25). In a comparative trial, sofosbuvir/velpatasvir yielded a higher sustained virological response rate than sofosbuvir/ribavirin (99% versus 94%), and this difference was statistically significant (25). In patients from Eastern Europe in particular, the possibility of an HCV-2k/1b chimera must be considered: this is a virus isolate with the characteristics of HCV genotype 2 at the 5' end (leading to classification as HCV genotype 2

in HCV typing assays), but those of HCV genotype 1 at the 3' end (and therefore also at the target area of all direct antiviral agents) (e24). For such chimeras, the sustained virological response rates are 30% with sofosbuvir/ribavirin (for twelve weeks) and more than 90% with sofosbuvir/NS5A inhibitor (for twelve weeks) (e24, e25) (personal communication from Dr. David Metreveli, European Limbach Diagnostic Group, Tbilisi, Georgia).

The treatment options for patients infected with HCV genotype 3 who have been previously treated with (peg-)interferon/ribavirin are the following:

- sofosbuvir/ribavirin for 24 weeks (sustained virological response rates, 71–87 %) (20, 25)
- sofosbuvir/daclatasvir or sofosbuvir/velpatasvir, for 12 weeks in both cases (sustained virological response rates of 86% and 91%, respectively) (21, 25).

The currently approved NS3/4A protease inhibitors simeprevir, paritaprevir and grazoprevir have no antiviral activity against HCV genotype 3 at the doses in which they are used. For patients who tolerated initial treatment with (peg-)interferon/ribavirin well, the combination (peg-)interferon/ribavirin/sofosbuvir is an alternative regimen for retreatment, with a sustained virological response rate of 94% (29).

Numerous drug regimens have been approved for the retreatment of patients infected with HCV genotype 4 (Table 2), while less evidence is available for the treatment of HCV genotypes 5 and 6 (e26, e27). In the latter situation, the pangenotypic combination sofosbuvir/velpatasvir can be given (24).

Virological relapse after interferon-free treatment with direct antiviral agents

Treatment failure during or after the administration of direct antiviral agents (DAA) is presumed to be due to the selection of resistance-associated viral variants (RAVs). The demonstrability of the different kinds of RAV by population-based sequencing, and their persistence rates, differ depending on the time of testing and the DAA substance class. RAVs in the NS5A gene generally persist longer than RAVs in the NS3/4A gene (30). All currently approved DAAs, with the exception of the nucleoside polymerase inhibitor sofosbuvir, have a relatively low resistance barrier, and there are relevant cross-resistances between the individual NS3/4A proteases and the NS5A inhibitors (30, e28).

HCV genotype 2 or 3 infection

The standard treatment of HCV genotype 2 infection is with sofosbuvir/ribavirin, and that of HCV genotype 3 infection is with sofosbuvir/daclatasvir, for twelve weeks in both cases.

Direct antiviral agents

Treatment failure during or after the administration of direct antiviral agents (DAA) is presumed to be due to the selection of resistance-associated viral variants (RAVs).

TABLE 2

Approved antiviral treatment regimens*

	Patients without hepatic cirrhosis		Patients with hepatic cirrhosis	
	Not previously treated	Previously treated	not previously treated	Previously treated
Fixed drug combinations				
Sofosbuvir/ledipasvir	HCV-1: 8–12 weeks* ¹ HCV-4: 12 weeks	HCV-1: 12 weeks HCV-4: 12 weeks	HCV-1: 12 weeks ± RBV* ² HCV-4: 12 weeks ± RBV* ²	HCV-1: 12 weeks + RBV* ³ HCV-4: 12 weeks + RBV* ³
Sofosbuvir + velpatasvir	HCV-1, -2, -3, -4, -5, -6: 12 weeks		HCV-1, -2, -3, -4, -5, -6: 12 weeks* ⁴	
Paritaprevir/r, ombitasvir, Dasabuvir	HCV-1a: 12 weeks + RBV HCV-1b: 8–12 weeks* ⁵		HCV-1a: 24 weeks + RBV HCV-1b: 12 weeks ± RBV* ⁶	
Paritaprevir/r, ombitasvir	HCV-4: 12 weeks + RBV		HCV-4: 12 weeks + RBV	
Grazoprevir + elbasvir	HCV-1a:12 weeks (16 weeks + RBV for patients with NS5A-RAVs at position 28, 30, 31, 58, or 93) HCV-1b:12 weeks HCV-4: 12 weeks (16 weeks + RBV for patients with a viral burden >800 000 IU/mL)			
Individual combinations				
Sofosbuvir + ribavirin	HCV-2: 12 weeks HCV-3: 24 weeks		HCV-2: 12 weeks HCV-3: 24 weeks	HCV-2: 12–16 weeks
Sofosbuvir + simeprevir	HCV-1: 12 weeks HCV-4: 12 weeks		HCV-1: 24 weeks ± RBV HCV-4: 12–24 weeks ± RBV	HCV-1: 24 weeks ± RBV HCV-4: 12–24 weeks ± RBV
Sofosbuvir + daclatasvir	HCV-1: 12 weeks HCV-3: 12 weeks HCV-4: 12 weeks		HCV-1: 24 weeks ± RBV HCV-3: 24 weeks ± RBV HCV-4: 24 weeks ± RBV	HCV-1: 24 weeks ± RBV HCV-3: 24 weeks + RBV HCV-4: 24 weeks ± RBV

* The information given here corresponds to the text of the European approval statements for the drugs in question. For more detailed recommendations, see the S3 guideline of the German Society for Gastroenterology and Digestive and Metabolic Diseases (*Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten*, DGVS). For economic prescribing practices, see the relevant instructions of the German Joint Federal Committee (*Gemeinsamer Bundesausschuss*, G-BA).

*¹ Eight weeks suffice for patients with a viral burden <6 million IU/mL (18).

*² Combination with ribavirin (RBV) is recommended by the German guideline for patients with negative predictors.

*³ In patients for whom ribavirin is contraindicated, the treatment should be prolonged to 24 weeks.

*⁴ Combination with ribavirin can be considered for patients with HCV genotype 3 infection and compensated cirrhosis. All patients with decompensated cirrhosis should be given RBV.

*⁵ Eight weeks suffice for previously untreated patients who are infected with HCV genotype 1b (e20).

*⁶ In the study of Feld et al. (e35), 60 out of 60 patients with HCV-genotype-1b-associated hepatic cirrhosis obtained sustained viral eradication without combination with ribavirin. HCV, hepatitis C virus; RBV, ribavirin

Treatment failures in combination therapy with multiple DAAs often reflect a complex virological situation. A new treatment can be initiated in a specialized center on the basis of HCV resistance analysis (e29, 31).

Fixed double and triple drug combinations (a second-generation NS3/4A protease inhibitor plus a second-generation NS5A inhibitor, each with antiviral activity covering selected RAVs as well, with or without a nucleoside polymerase inhibitor) (e30–e32) are now in an advanced stage of clinical development.

They can achieve high rates of sustained viral eradication even in patients who have previously experienced a DAA treatment failure. These combinations are expected to be approved in 2017.

Compensated hepatic cirrhosis

Fibrosis in patients with chronic hepatitis C is now staged non-invasively by means of biochemical algorithms (the APRI score, FIB4, and others) or elastographic techniques (e33, e34). The sensitivity and specificity of transient elastography for the diagnosis of

Failure of combination therapy

Treatment failures in combination therapy with multiple DAAs often reflect a complex virological situation.

Triple combination therapies

Triple drug combinations are now in an advanced stage of clinical development. They can achieve high rates of sustained viral eradication even in patients who have previously experienced a DAA treatment failure.

hepatic cirrhosis (threshold value of liver stiffness, 12.5 kPa) are 83–87% and 89–95%, respectively (e34).

In patients infected with HCV genotype 1 who have not been previously treated, the following approved antiviral treatment regimens can be used regardless of whether the patient has or does not have compensated hepatic cirrhosis:

- sofosbuvir/ledipasvir (10, 32)
- sofosbuvir/velpatasvir (11, 24)
- grazoprevir/elbasvir (14, 23)
- paritaprevir/ombitasvir/dasabuvir in HCV genotype 1b infection (33, e35)

In cirrhotic patients with HCV genotype 1a infection, it is recommended that treatment with paritaprevir/ombitasvir/dasabuvir should be prolonged from 12 to 24 weeks, with the concomitant administration of ribavirin (12, 13, 33). The phase 3 trials of sofosbuvir/simeprevir did not include the concomitant administration of ribavirin. In patients infected with HCV genotype 1a with a polymorphism at position 80 of the NS3/4A protease (Q80K), the antiviral efficacy of simeprevir is reduced; the sustained virus eradication rate for sofosbuvir/simeprevir without ribavirin in this patient group is only 74% (e36). There are conflicting data on the combination of sofosbuvir/daclatasvir with ribavirin (1, e37).

For previously treated patients infected with HCV genotype 1 who have compensated hepatic cirrhosis, it is recommended that sofosbuvir/ledipasvir should be given for the usual duration of 12 weeks, but with concomitant ribavirin administration. If ribavirin is not tolerated, the treatment should be prolonged to 24 weeks (10, e38–e41). For the grazoprevir/elbasvir treatment regimen in patients infected with HCV genotype 1a, concomitant ribavirin treatment and a prolongation of the treatment from 12 to 16 weeks should be considered (e42). For other treatment regimens, the recommendations are no different for previously untreated and previously treated patients with cirrhosis.

The highest sustained virological response rates in cirrhotic patients infected with HCV genotype 2 were achieved with sofosbuvir/velpatasvir independently of previous treatment (25). For patients infected with HCV genotype 3, data from a trial on patients with decompensated hepatic cirrhosis (34) make it seem reasonable to give ribavirin concomitantly to patients with compensated hepatic cirrhosis as well; the approval text is formulated in such a way as to permit this option (11). An alternative treatment regimen is sofos-

buvir/daclatasvir, but the evidence from phase 3 trials on the duration of treatment and the concomitant administration of ribavirin is currently incomplete (21, e43). For patients infected with HCV genotype 3 who have compensated hepatic cirrhosis, a further therapeutic option is the combination peginterferon/ribavirin/sofosbuvir for 12 weeks (with a sustained viral eradication rate of 91% in previously untreated patients, 86% in previously treated patients) (29).

The spectrum of available treatments for patients infected with HCV genotype 4 largely corresponds to that of patients infected with HCV genotype 1 (Table 2). Sofosbuvir/velpatasvir has been approved for the treatment of patients infected with HCV genotypes 5 and 6 with compensated hepatic cirrhosis, although the evidence base is inadequate for more specific recommendations in relation to previous treatment (11, 24).

Decompensated hepatic cirrhosis

Precirrrosis and compensated cirrhosis can be hard to distinguish on clinical grounds, but decompensated cirrhosis is well defined. In patients with decompensated cirrhosis, NS3/4A protease inhibitors and non-nucleoside polymerase inhibitors should not be used, as their pharmacokinetic characteristics may cause further liver damage (12–14, 16). This consideration limits the antiviral treatment options for such patients to sofosbuvir and the combinable NS5A inhibitors (1, 2, 34, 35).

There is a clear indication for antiviral treatment in all patients for whom liver transplantation can be avoided in the intermediate or long term. The issue is more complex in patients for whom liver transplantation is already held to be indicated. The advantages of viral eradication before transplantation (more favorable perioperative course, prevention of reinfection of the transplanted organ) must be weighed against the potential adverse effects of antiviral drugs in patients with decompensated cirrhosis (possible higher infection rate, lactic acidosis) and the potential influence of successful viral eradication on organ allocation priorities (improved MELD, and thus lower priority, in a patient still needing liver transplantation) (3, e44, e45). Thus, the decision to give antiviral treatment to patients on the waiting list for liver transplantation should only be made after consultation with the transplant center. Ribavirin should be given concomitantly to optimize antiviral efficacy, but at a lower initial dose (600 mg/day) in patients with decompensated cirrhosis.

Cirrhotic patients infected with HCV genotype 2

The highest sustained virological response rates in cirrhotic patients infected with HCV genotype 2 were achieved with sofosbuvir/velpatasvir independently of previous treatment.

Patients infected with HCV genotype 4

The spectrum of available treatments for patients infected with HCV genotype 4 largely corresponds to that of patients infected with HCV genotype 1.

HCV-associated hepatic cirrhosis with hepatocellular carcinoma (HCC)

Any treatment of HCC with curative intent should be accompanied by antiviral treatment with the goal of viral eradication. Although there is a role for antiviral suppression therapy in the palliative treatment of hepatitis-B-associated HCC (e46), there are no analogous data regarding the palliative treatment of HCV-associated HCC. The decision to give antiviral treatment should be made in an experienced center on an individual basis, in consideration of the overall treatment concept and the patient's life expectancy (3).

After liver transplantation

The progression of fibrosis due to chronic hepatitis C is accelerated in patients who are immune-suppressed after liver transplantation; thus, as a rule, antiviral treatment is indicated. Patients with fibrosing cholestatic hepatitis have a higher mortality and should therefore be started on antiviral treatment immediately. In transplant recipients with a mild HCV (re-)infection, antiviral treatment can be initiated after glucocorticoids have been discontinued (3). Antiviral treatment can also be clinically indicated for the differential diagnosis of an acute rejection reaction. The antiviral treatment options correspond to those of patients who are not transplant recipients (1, 35, e47, e48), but the antiviral drugs should be selected with due regard to potential interactions (immunosuppressants), comorbidities, and ribavirin side effects (36).

End-stage and near-end-stage renal failure

The safety of sofosbuvir for patients with severe renal insufficiency (glomerular filtration rate $<30 \text{ mL/min/1.73m}^2$) or patients receiving hemodialysis because of end-stage renal failure has not been adequately demonstrated. A single dose of 400 mg of sofosbuvir in such patients leads to a marked rise in the plasma level of sofosbuvir and of its metabolite GS-331007 (15).

Approved antiviral treatment regimens for patients with severe renal insufficiency include paritaprevir/ombitasvir with or without dasabuvir (for patients with HCV genotype 1 or 4 infection, respectively) and grazoprevir/elbasvir for patients with HCV genotype 1 or 4 infection (12–14, 37, 38). Ribavirin is recommended in analogy to patient groups with normal renal function, but at a lower dose (200 mg/day).

Because of the lack of approved options for antiviral treatment, patients infected with HCV genotype 3 have also been treated off-label with combinations contain-

ing sofosbuvir, with very good virological response rates. No severe side effects have been noted in the small patient cohorts published to date (e49, e50).

Coinfected patients

Patients with an HCV mono-infection and those with an HCV/HIV coinfection do not differ with respect to their sustained viral eradication rates or side-effect profiles with interferon-free DAA treatment (e51–e54). Prescribing physicians should note potential drug interactions between the various HCV treatment regimens (in particular, those involving NS3/4A protease inhibitors) and the antiretroviral drugs given to treat HIV (36). In HBV/HCV coinfection, the hepatitis virus with the higher viral load is treated with higher priority. The sustained virus eradication rates in the treatment of chronic hepatitis C are not lessened by the simultaneous presence of hepatitis B (e55). There are no clinically relevant drug interactions between DAAs against HCV on the one hand, and tenofovir and entecavir on the other.

Antiviral treatment in pregnancy

The risk of vertical transmission in mothers with an HCV mono-infection is 5% and is not diminished by cesarean section (e56). Mothers are not advised against breastfeeding either. Vertically acquired hepatitis C takes a mild course in childhood, with very slow progression of hepatic fibrosis (e57). Antiviral treatment during pregnancy cannot be recommended, as there are insufficient data on the potential teratogenicity of DAAs.

Antiviral treatment in childhood

In an initial clinical trial, 12 weeks of treatment with sofosbuvir/ledipasvir (400 mg / 90 mg) yielded sustained virus eradication rates of 96% and 100% in patients aged 12 to 17 (body weight 33–128 kg) with chronic HCV infection of genotypes 1 and 4, respectively. The pharmacokinetic parameters of both substances were analogous to those seen in adults (e58). Further cohorts of children aged 6–11 (17–44 kg) and 3–5 (<17 kg) are now under evaluation, with drug doses of 33.75–45 mg (ledipasvir) and 150–200 mg (sofosbuvir) (e59). The findings are expected to become available in 2017.

Preemptive HCV treatment before immunotherapy or chemotherapy

There is an urgent indication for preemptive antiviral treatment in patients with a chronic hepatitis B infection before they undergo certain types of immunotherapy or

After liver transplantation

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Pregnancy

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chemotherapy (in particular, before treatment with anti-CD20 antibodies) (e60). There is insufficient evidence at present for any recommendation of an analogous procedure for patients with chronic hepatitis C.

Important side effects and drug interactions

Sofosbuvir is generally well tolerated; its more common side effects include mild nausea, headache, and insomnia (15). The combination of sofosbuvir with amiodarone can cause life-threatening bradycardia (39). The addition of NS5A inhibitors (ledipasvir, daclatasvir, velpatasvir) does not lessen tolerability to any clinically relevant extent (10, 11). Therapeutic elevation of the gastric pH lessens the bioavailability of ledipasvir, and thus the concomitant administration of sofosbuvir/ledipasvir with a proton pump inhibitor in a high dose is not recommended (e61).

The side-effect profile and drug-interaction spectrum of the NS3/4A protease inhibitors are more complex. Simeprevir can evoke both nonspecific side effects (nausea, headache, fatigue) and photosensitivity reactions; patients should be advised to avoid direct exposure to sunlight and to use a topical sunscreen (16). All of the approved NS3/4A protease inhibitors (simeprevir, paritaprevir, grazoprevir) can mildly or moderately elevate bilirubin and transaminase levels (12, 14, 16). A simultaneous, clinically relevant rise of both the bilirubin concentration and the transaminase concentrations is rare but presumably reflects hepatotoxicity and must be followed by discontinuation of the protease inhibitor. The characteristic side effects of ribavirin are (dose-dependent) hemolytic anemia, dyspnea, an irritative cough, reduced exercise tolerance, and skin rash (40). As hemolysis elevates the bilirubin concentration as well, rises in bilirubin levels are more pronounced when ribavirin and NS3/4A protease inhibitors are given simultaneously.

All drugs taken for concurrent illnesses should also be checked for possible interactions with antiviral drugs against HCV (see the relevant package inserts and the website maintained by the pharmacology department at the University of Liverpool, www.hep-druginteractions.org) (36). Particularly critical classes of drugs include anticonvulsants, anti-arrhythmic drugs, antimycobacterial drugs, St. John's wort, and—in combination with NS3/4A protease inhibitors—immunosuppressant drugs, antibiotics, antimycotic drugs, antiretroviral drugs, HMG-CoA reductase inhibitors, sedatives, antidepressants, and antipsychotic drugs (36).

Conflict of interest statement

Prof. Zeuzem has received third-party funding for clinical trials from AbbVie, BMS, Boehringer Ingelheim, Gilead, Janssen-Cilag, Merck/MSD, Novartis, RochePharma, Santaris, Vertex, and ZymoGenetics. He serves as a scientific advisor for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck/MSD for questions concerning the treatment of hepatitis C and receives honoraria from these companies for lectures at continuing medical education events, as well as reimbursement of travel and accommodation expenses.

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Drug interactions

The combination of sofosbuvir with amiodarone can cause life-threatening bradycardia.

Information on drug interactions

Potential drug interactions with antiviral drugs against HCV can be checked on a website maintained by the pharmacology department at the University of Liverpool: www.hep-druginteractions.org

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Further information on CME

This article has been certified by the North Rhine Academy for Postgraduate and Continuing Medical Education. Deutsches Ärzteblatt provides certified continuing medical education (CME) in accordance with the requirements of the Medical Associations of the German federal states (Länder). CME points of the Medical Associations can be acquired only through the Internet, not by mail or fax, by the use of the German version of the CME questionnaire. See the following website: cme.aerzteblatt.de.

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This CME unit can be accessed until 2 April 2017, and earlier CME units until the dates indicated:

- “the Differential Diagnosis of Dyspnea” (Issue 49/2016) until 5 March 2017,
- “Head Lice” (Issue 45/2016) until 5 February 2017.

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Supplementary material:
eReferences:
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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the most appropriate answer.

Question 1

What is the incidence of hepatocellular carcinoma in patients with HCV-associated hepatic cirrhosis?

- a) 0–2%
- b) 3–6%
- c) 7–10%
- d) 11–14%
- e) 15–18%

Question 2

What is the chronification rate of acute hepatitis C?

- a) <10%
- b) 20%
- c) 30%
- d) 40%
- e) >50%

Question 3

How long should patients with acute hepatitis C be treated?

- a) 2 weeks
- b) 4 weeks
- c) 8 weeks
- d) 12 weeks
- e) 24 weeks

Question 4

At what point in the replication cycle of the hepatitis C virus do NS3/4A protease inhibitors exert their effect?

- a) receptor binding and endocytosis
- b) transport and release
- c) RNA replication
- d) translation and polyprotein processing
- e) virion assembly

Question 5

In what combined treatment for hepatitis C can the doses of the agents be chosen freely?

- a) sofosbuvir + daclatasvir
- b) sofosbuvir + ledipasvir
- c) sofosbuvir + velpatasvir
- d) paritaprevir/ritonavir + ombitasvir
- e) grazoprevir + elbasvir

Question 6

What treatment regimen for hepatitis C has pangenotypic activity?

- a) sofosbuvir + simeprevir
- b) sofosbuvir + ledipasvir
- c) sofosbuvir + velpatasvir
- d) paritaprevir/ritonavir + ombitasvir
- e) grazoprevir + elbasvir

Question 7

What drug is contraindicated for patients with decompensated hepatic cirrhosis?

- a) sofosbuvir
- b) grazoprevir
- c) ledipasvir
- d) velpatasvir
- e) ribavirin

Question 8

For which drug are there currently insufficient data on its use to treat hepatitis C patients with severe renal insufficiency?

- a) simeprevir
- b) paritaprevir/ritonavir
- c) dasabuvir
- d) daclatasvir
- e) sofosbuvir

Question 9

What drug can cause life-threatening bradycardia if given to a patient taking sofosbuvir for the treatment of hepatitis C?

- a) carvedilol
- b) spironolactone
- c) amlodipine
- d) amiodarone
- e) citalopram

Question 10

Why should sofosbuvir/ledipasvir not be given together with a high-dosed proton pump inhibitor?

- a) elevated risk of reflux
- b) shared metabolic pathway (cytochrome P450 1A2)
- c) elevated risk of renal failure
- d) elevated risk of liver damage
- e) diminished bioavailability of ledipasvir

Supplementary material to:

Treatment Options in Hepatitis C

The Current State of the Art

by Stefan Zeuzem

Dtsch Arztebl Int 2017; 114:11–21. DOI: 10.3238/arztebl.2017.0011

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