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Abstract
Chronic hepatitis C virus (HCV) infection affects 80-160 million people worldwide and is one of the leading causes of chronic liver disease. It is only a few years ago that standard treatment regimes were based on pegylated interferon alpha and ribavirin. However, treatment of HCV has undergone a revolutionary change in recent years. The admission of the nucleotide polymerase inhibitor Sofosbuvir enabled an interferon-free regimen with direct antiviral agents (DAA). Meanwhile seven DAAs are available and can be applied in several combinations for 8 to 24 wk depending on HCV genotype and patient characteristics such as cirrhosis and chronic renal failure. High rates of sustained virological response (SVR) rates can be achieved with these novel drugs. Even in difficult to treat populations such as patients with liver cirrhosis, HCV-human immunodeficiency virus co-infections, after liver transplantation, or with chronic kidney disease comparable high rates of SVR can be achieved. The anticipated 2nd generation DAAs are strikingly effective in patients so far classified as difficult to treat including decompensated liver cirrhosis or post-transplant patients. These 2nd generations DAAs will have higher resistance barriers, higher antiviral effects and a pan-genotypic spectrum. This review highlights the current state of the art of antiviral treatment in hepatitis C and gives an outlook for upcoming therapies.

Key words: Hepatitis C virus; Direct antiviral agents; Sustained virological response; Liver transplantation; Renal impairment; Cirrhosis

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Core tip: Treatment of chronic hepatitis C virus (HCV) infections has undergone a revolutionary change in recent years. This review highlights the current state of the art of antiviral treatment in chronic hepatitis C infections and gives an outlook for upcoming therapies. Difficult to treat populations such as patients with decompensated liver cirrhosis, HCV-human immunodeficiency virus co-infections, after liver transplantation and patients with renal impairment or on hemodialysis are highlighted.
INTRODUCTION

Chronic hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease worldwide[1]. Worldwide 80-160 million people are estimated to be chronically infected with HCV[2]. The long-term follow of chronic HCV are highly variable, ranging from minimal histological changes to extensive fibrosis with or without cirrhosis[2].

The primary goal of HCV therapy is to achieve eradication of the HCV which is currently determined by a sustained virological response (SVR) as surrogate marker. SVR is defined as undetectable HCV RNA 12 wk (SVR 12) or 24 wk (SVR 24) after end of treatment.

In recent years antiviral therapy has experienced a tremendous progress. It is only a few years ago that standard treatment regimes were based on pegylated interferon alpha and ribavirin (P/R). These therapies were associated with many adverse effects, long treatment durations of usually 48 wk and low SVR rates[3,4]. In 2011, the two protease inhibitors boceprevir and telaprevir were approved for treatment of genotype 1. Due to their comparatively lower antiviral effectiveness and rapid resistance development both drugs were used only as triple-therapy regimen in combination with pegylated interferon alpha and ribavirin[5-8].

Since 2014 several direct acting antivirals (DAAs) have been approved enabling interferon-free antiviral treatments with high SVR rates.

The decoding of the HCV life cycle and the resolution of crystal structure of the relevant viral proteins enabled the development of many DAAs. The currently approved DAAs consist of three groups. The first group is directed against the viral protease NS3/4A (protease inhibitors; name ending on -previr), the second against the viral RNA-dependent RNA-polymerase NS5B (polymerase inhibitors; name ending on -buvir) and the third against the viral protein which is involved in the formation of the replicon complex NS5A (NS5A-inhibitors, name ending on -asvir)

DAA SUBSTANCES

Sofosbuvir

Sofosbuvir (SOF) is an inhibitor of the NS5B-polymerase. As nucleotide analogue it causes chain termination during replication. SOF has a pan-genotypic effectiveness and a high resistance barrier. It is taken once daily with a good tolerability. No cross resistances with other substances have been reported. Drug interactions were described only for strong inducers of the gut transporters P-gp and BCRP (e.g., rifampicin, St John’s wort, carbamazepin, phenytoin)[10].

Simeprevir

Simeprevir (SMV) is a second-generation protease inhibitor. In addition to the activity against genotype 1 a simeprevir has clinically relevant antiviral effects against genotypes 4 and 6. Similar to boceprevir it needs to be taken only once a day. Adverse effects reported in clinical studies consisted mainly of skin lesions with or without itching, nausea and dyspnea. Of note, the variant (RAV) Q80K exhibits a preexisting resistance against simeprevir resulting in treatment failure of patients with genotype 1a[11].

As SMV is metabolized by hepatic CYP3A4, inhibitors and inductors of CYP3A4 may affect plasma levels of SMV[12].

Daclatasvir

Daclatasvir (DCV) is a NS5A-inhibitor. DCV has a high antiviral activity against genotypes 1 to 4 in vivo and in vitro also against genotypes 5 and 6. On the other side the resistance barrier is relatively low. In case of treatment failure resistance-associated resistances (RAVs) may be selected, which remain detectable after end of treatment[13]. The influence of these RAVs on following therapies has not been systematically investigated so far. In studies using P/R the combination of DCV plus P/R showed no additional adverse effects[14].

Similar to SMV, DCV is also metabolized by CYP3A4.

Ledipasvir

Ledipasvir (LDV) represents another NS5A-inhibitor with antiviral activity particularly against genotype 1 and partially against other genotypes such as 4-6. LDV is only available in a fix dose combination with SOF. The most commonly reported adverse effects were headache and fatigue. As with DCV, RAVs have been detected during therapy and were not clinically relevant due to the strong antiviral effect of SOF[15].

In vitro, no detectable metabolism of ledipasvir was observed by human CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Evidence of slow oxidative metabolism via an unknown mechanism has been observed. Bilary excretion of unchanged ledipasvir is a major route of elimination, with renal excretion being a minor pathway (approximately 1%).

Paritaprevir/ritonavir + ombitasvir ± dasabuvir

The combination of paritaprevir/ritonavir (PTV/r) + ombitasvir (OBV) ± dasabuvir (DSV) is referred to as 3D. PTV is an NS3/4A-inhibitor, which is boosted by r to optimize its pharmacokinetics. OBV is an NS5A-inhibitor, while DSV is a non-nucleotide polymerase-inhibitor. PTV/r and OBV are available at fix dose combinations and have antiviral activity against genotypes 1 and 4, while DSV is only effective against genotype 1. Registered adverse effects were pruritus in clinical study cohorts.
Table 1  Current recommendations of antiviral regimens depending on the genotype

| DAA-regime                  | HCV-genotype |
|-----------------------------|--------------|
|                             | 1a 1b 2 3 4 5 6 |
| SOF + R                     | × × × × × × |
| SOF + SMV ± R               | × × × × × × |
| SOF + DCV ± R               | × × × × × × |
| SOF + LDV ± R               | × × × × × × |
| OBV + PTV/r ± DSV ± R (3D)  | × × × × × × |
| OBV + PTV/r ± R (2D)        | × × × × × × |

1DCC, no approval in the United States. DAA: Direct antiviral agents; LDV: Ledipasvir; SMV: Simeprevir; DCV: Daclatasvir; SOF: Sofosbuvir; OBV: Ombitasvir; PTV: Paritaprevir; HCV: Hepatitis C virus; DSV: Dasabuvir; R: Ritonavir.

With ribavirin and in very few patient increased transaminases as well as elevations of bilirubin. As PTV/r is metabolized by CYP3A4 interactions with several other drugs may occur. There are existing cross-resistances to other protease-inhibitors and NSSA-inhibitors while DSV has a low resistance-barrier.

DAA COMBINATION REGIMENS

Of the approved DAs the following combinations have been studied in clinical trials (Table 1).

SOF is the so-called backbone of most combinations, as it has a high resistance barrier and a pan-genotypic activity. In contrast, the high antiviral activity is achieved by the combination of the various groups of substances in the 3D-regime. In all regimes the addition of R is possible and may be useful for defined patient groups.

### SOF + R

This combination has high SVR-rates (86%-97%) in genotype 2 patients[10,17]. In genotype 1, however, SVR-rates were inconsistently in phase 2 studies. Especially in difficult to treat patients, e.g., with cirrhosis, SVR-rates were unsatisfactory (SVR 10%-84%)[18]. Furthermore, genotype 3 treatment efficacy during a 12-wk regimen was low with SVR rates between 30% to 56%[10,17]. However, a significant increase in SVR-rates up to 85% could be achieved by extending the treatment duration to 24 wk in patients with genotype 3. Existence of cirrhosis was associated with poorer SVR-rates in genotype 3 patients (SVR 68% with cirrhosis and pretreatment with P/R vs SVR 91% without cirrhosis)[19]. Smaller studies treating genotype 4 patients for 12 and 24 wk, respectively, have shown SVR-rates in therapy-naive patients of 79% and 100%, respectively, and in pretreated patients 59% and 87%, respectively[20].

### SOF + SMV ± R

The COSMOS-study, a phase II trial, analyzed the efficacy of SOF + SMV with and without R in patients with HCV genotype 1. This study consisted of two cohorts of which the first represented patients with null-response to P/R but without advanced fibrosis or cirrhosis. The second cohort included patients with advanced fibrosis (F3) or cirrhosis. Patients were treated for 12 or 24 wk with and without R. In the first cohort a cumulative SVR of 90% was observed, while in the second cohort an even higher SVR of 94% could be achieved. Neither the extension to a 24-wk treatment nor the addition of R were of any advantage in this study[21].

These results could be confirmed by two big observational-studies. The TRIO-trail was able to demonstrate a higher SVR in genotype 1b, compared to 1a (92% vs 80%)[21]. The TARGET-study with 883 genotype 1 patients (54% cirrhosis) treated with SOF + SMV ± R presented in an interim analysis a SVR4-rate of 93% in 98 patients without cirrhosis and in patients a SVR4 of 85% in 124 cirrhotics[22].

Meanwhile results of two phase-III study entitled OPTIMIST 1 and 2 have been presented. In the OPTIMIST 1-study 310 naïve or pretreated genotype 1 patients without cirrhosis were treated with SOF + SMV for 8 or 12 wk. Patients treated for 12 wk achieved SVR-rates of 97% and those treated only for 8 wk 83%[23]. The OPTIMIST 2-study investigated 103 naïve or pretreated genotype 1 patients with cirrhosis being treated for 12 wk with SOF + SMV resulting in a SVR of 83%[24].

### SOF + DCV ± R

The combination of SOF + DCV was investigated in treatment-naïve patients with genotypes 1, 2 and 3 without cirrhosis and in genotype 1-patients with treatment-failure of a protease-inhibitor based therapy. The treatment response in GT1 was investigated in different groups in a phase II-study. The results showed high SVR-rates between 93%-100% regardless of treatment duration and addition of R. In pretreated genotype 1 patients only 24 wk of therapy were evaluated with or without R. This regimen resulted in SVR-rates of 95%-100% The ALLY-1 study investigated SOF + DCV + R for 12 wk in patients with cirrhosis (n = 60) or after orthotopic liver-transplantation (OLT) (n = 53). For genotype 1, patients with cirrhosis achieved a SVR rate of 82%, whereas the SVR rate after OLT was even higher with 95%[25].

Initially only a 24-wk treatment was evaluated in genotype 2 and 3 patients. This lead to SVR rates of 92% in genotype 2 and 89% in genotype 3 patients[26]. In the ALLY-3 study genotype 2 patients were treated with SOF + DCV for 12 wk without R. Patients without cirrhosis achieved independent of pretreatment high SVR-rates of 97% in naïve and 94% in pretreated patients. In case of cirrhosis SVR rates were lower with only 58% to 69%[27]. The combination of SOF and DCV has an antiviral effectiveness in genotype 4 but results of studies are lacking.

### SOF + LDV ± R

For this fixed dose combination profound phase 3 study data exists. Studies were performed on 1.952 patients...
Table 2 Overview on clinical studies using the NSSB inhibitor sofosbuvir

| Study  | Patient population | Therapy                  | Duration (wk) | SVR  | Comments |
|--------|--------------------|--------------------------|---------------|------|----------|
| ION-1  | First-line therapy | SOF + LDV                | 12            | 99%  |          |
|        |                    | SOF + LDV + R            | 12            | 97%  |          |
|        |                    | SOF + LDV                | 24            | 98%  |          |
|        |                    | SOF + LDV + R            | 24            | 99%  |          |
| ION-2  | Re-therapy         | SOF + LDV                | 12            | 94%  | 86% cirrhotic |
|        |                    | SOF + LDV + R            | 12            | 96%  | 82% cirrhotic |
|        |                    | SOF + LDV                | 24            | 99%  | 100% cirrhotic |
|        |                    | SOF + LDV + R            | 24            | 99%  | 86% cirrhotic |
| ION-3  | First-line therapy | SOF + LDV                | 8             | 94%  | Only non-cirrhotic |
|        |                    | SOF + LDV + R            | 8             | 93%  | Only non-cirrhotic |
|        |                    | SOF + LDV                | 12            | 95%  | Only non-cirrhotic |

SOF: Sofosbuvir; LDV: Ledipasvir; R: Ribavirin; SVR: Sustained virological response.

Table 3 Overview on clinical studies using the combination of paritaprevir/ritonavir + ombitasvir ± dasabuvir

| Study              | Patient population | Therapy                  | Duration (wk) | SVR  | Comments |
|--------------------|--------------------|--------------------------|---------------|------|----------|
| SAPPHIRE-I         | First-line therapy | OBV + PTV/r + DSV + R    | 12            | 96%  | No cirrhosis |
| SAPPHIRE-II        | Re-therapy         | OBV + PTV/r + DSV + R    | 12            | 96%  | No cirrhosis |
| TURQUOISE-II       | Cirrhosis          | OBV + PTV/r + DSV + R    | 12            | 92%  | GT1a 89% GT1b 99% |
|                    |                    | OBV + PTV/r + DSV + R    | 24            | 96%  | GT1a 95% GT1b 100% |
| PEARL-II           | Re-therapy, GT1b   | OBV + PTV/r + DSV        | 12            | 100% | No cirrhosis |
| PEARL-III          | First-line therapy, GT1b | OBV + PTV/r + DSV | 12            | 97%  | No cirrhosis |
| PEARL-IV           | First-line therapy, GT1a | OBV + PTV/r + DSV | 12            | 99%  | No cirrhosis |
|                    |                    | OBV + PTV/r + DSV + R    | 12            | 90%  | No cirrhosis |
|                    |                    | OBV + PTV/r + DSV + R    | 12            | 97%  | No cirrhosis |

OBV: Ombitasvir; PTV: Paritaprevir; DSV: Dasabuvir; R: Ribavirin; r: Ritonavir; SVR: Sustained virological response.

with genotype 1. The detailed results of the ION-studies are shown in Table 2. In all treatment-groups high rates of SVR were observed. In treatment-naïve patients there was neither advantage of treatment for more than 12 wk nor addition of R even in cirrhotic patients. In contrast, pretreated patients with cirrhosis achieved higher SVR-rates after treatment for 24 wk. In these patients high SVR-rates could also be achieved by adding R to a 12 wk antiviral treatment.

Treatment-naïve genotype 1-patients without cirrhosis achieved a SVR of 94% after only 8 wk of treatment. The higher number of relapses in this cohort were patients with a viral load above $6 \times 10^6$ IU/mL.

For genotypes 3 and 6 data from a small study showed also a high antiviral effectiveness for SOF/LDV + R. Genotype 3 treatment-naïve patients with cirrhosis achieved 100% SVR, pretreated patients with cirrhosis 89% SVR. Without addition of R only 64% of the treatment-naïve cirrhotic patients achieved SVR. In genotype 6 SOF/LDV without R resulted in SVR-rates of 96%.

$\text{OBV + PTV/r } \pm \text{ DSV } \pm \text{ R (3D)}$

The 3D-regimen achieved high SVR-rates in several phase III-studies with a total of 1577 genotype 1 patients. The detailed results of these studies are shown in Table 3. The 3D-regimen achieved in genotype 1 patients without cirrhosis in the SAPPHIRE-study high SVR-rates of 96% regardless of a prior therapy.

Due to a weaker antiviral activity of 3D in genotype 1a the PEARL-studies (which did not include cirrhotic patients) were performed separately for both subtypes. The treatment-regimes differed regarding the addition of R. In genotype 1b nearly all patients achieved SVR without R regardless of pretreatment indicating that R can be omitted for this patient population.

In contrast, genotype 1a patients exhibited higher SVR-rates by addition of R compared to those being treated without R (97% vs 90%).

Genotype 1 patients with cirrhosis were investigated in the TURQUOISE-II-study. Here, 3D + R was admitted for 12 or 24 wk. For genotype 1a extension of treatment from 12 to 24 wk resulted in higher SVR-rates (89% vs 95%), whereas for genotype 1b nearly all patients were cured by a 12-wk treatment.

In genotype 4 DSV was omitted due to lack of antiviral activity. Therefore, a combination of OBV + PTV/r with and without R was tested for 12 wk in the PEARL-I-study. Addition of R resulted in a SVR rate of 100%, whereas without R only 91% of patients
achieved SVR\textsuperscript{[36]}.

Current treatment recommendations have been published in the AASLD and EASL guidelines. These take into account the specific conditions in different countries in terms of availability of DAA\textsuperscript{s}\textsuperscript{[2,37]}. So far there are currently sufficient IFN-free DAA-regimes with excellent SVR-rates, in particular for genotype 1 patients. Unresolved issues represent patients with relapse after DAA-regimen as they exhibit RAVs and cirrhotic patients with genotype 3 as SVR rates remain unsatisfactory for this population. Current antiviral studies address these challenges and in the near future we expect efficient regimens for the remaining difficult to treat HCV patients.

**DIFFICULT TO TREAT POPULATIONS**

**Cirrhotic patients**

Liver cirrhosis is the most important negative predictor of SVR in DAA therapies. In nearly all regimens treatment efficacy is lower compared to non-cirrhotic patients. In pivotal studies on cirrhotic patients for the 3D-regime and SOF/LDV SVR could be increased by treatment extension to 24 wk and addition of ribavirin. It should be noted that only compensated patients with Child Pugh stage A were included in these studies. Recently, in a prospective study 108 patients with decompensated cirrhosis with Child Pugh stage B and C were treated with SOF/LDV + R for 12 or 24 wk. SVR was achieved in 87% of patients with Child Pugh B and 89% with Child Pugh C indicating that this therapy regimen is safe and effective even in decompensated liver cirrhosis. Of note, an improvement of liver function was observed during and after therapy\textsuperscript{[39]}.

**Liver transplantation**

After liver transplantation of patients with chronic HCV infections a reinfection is common. Due to immunosuppression an accelerated progression of fibrosis in the transplant is often observed. Pre-treatment with SOF + R before transplantation in 61 patients with HCC within Milan criteria and compensated HCV-induced cirrhosis prevented a reinfection of the graft in 70%\textsuperscript{[39]}. After liver transplantation a different study using the 3D-regime + R resulted in a SVR of 97% (33 out of 34 patients)\textsuperscript{[40]}. Using SOF/LDV + R for 12 or 24 wk in 223 patients after liver transplantation similar high SVR rates could be achieved in patients without cirrhosis (96%-98%) or Child Pugh A cirrhosis (96%). However, in case of decompensated cirrhosis SVR rates were lower (Child Pugh B: 83%-85%, Child Pugh C: 60%-67%)\textsuperscript{[41]}.

**Human immunodeficiency virus-HCV co-infection**

Human immunodeficiency virus (HIV)-HCV co-infections result in a faster progression of fibrosis compared to mono-infections. In a variety of studies with similar designs comparable treatment responses were found. Thus, HIV-HCV co-infected patients can be treated equal to mono-infected patients. To give an example the combination-therapy with SOF/LDV achieved SVR-rate of 98% in GT1 first line therapy\textsuperscript{[42]}. It should be noted that possible drug-drug interactions between HCV regimes and antiretroviral substances may occur.

**Renal impairment**

Due to its renal elimination SOF may only be given to patients with a glomerular filtration rate above 30 mL/min per 1.73 m\textsuperscript{2}. Patients with severe renal impairment (glomerular filtration rate < 30 mL/min per 1.73 m\textsuperscript{2}) or chronic renal failure undergoing dialysis therefore require other antiviral regimens.

Pharmacokinetic data showed the possibility of using OBV + PTV/r + DSV ± R (3D) in patients with severe renal impairment and chronic renal failure. Serum levels of the 3D substances were comparable to HCV-patients without renal impairment. SVR12 data are outstanding but all finished patients (10 out of 20) presented SVR\textsuperscript{4[3]}. Another placebo-controlled study with Grazoprevir (100 mg) plus Elbasvir (50 mg) for 12 wk in 122 HCV GT 1 patients with renal impairment (75% under dialysis) presented SVR12 rates of 94%, representing a potential future treatment regimen in this difficult to treat patient population\textsuperscript{[44]}.

**FUTURE HCV TREATMENT OPTIONS**

Future developments consist of second generation DAAs. The protease inhibitors of the second generation will exhibit a better resistance barrier and broader spectrum of activity against various genotypes of HCV, in particular subtype 1a (e.g., Grazoprevir, Sovalprevir) and pan-genotypic (e.g., ABT-493, GS-9857). Moreover, these substances do not have complete cross-resistances against associated RAVs against first-generation protease inhibitors (e.g., ABT-493)\textsuperscript{[45]}. The second generation NSSA-inhibitors will have higher resistance barriers, higher antiviral effects and a pan-genotypic spectrum (e.g., Elbasvir, Samatasvir, GS-5816, MK-8408, ABT-530). ABT-530 presented in vitro high antiviral effectiveness against frequent NSSA-RAVs\textsuperscript{[45]}. Furthermore, novel drugs will be used as combination-regimes. Combinations of these protease inhibitors and NSSA-inhibitors could achieve similar SVR-rates than previous regimes based on nucleotide NS5B-polymerase inhibitors (NUC). It is likely that shorter treatment durations may be achieved using these regimes. A recently presented study using Grazoprevir/Elbasvir + SOF (C-SWIFT) in treatment-naïve genotype 1 and 3 patients with and without cirrhosis investigated the antiviral effectiveness in terms of treatment duration. In genotype 1 non-cirrhotic patients achieved SVR in only 33% after 4 wk of treatment. In contrast, an SVR-rate of 87% was achieved after 6 wk of treatment. Cirrhotic patients with HCV-genotype 1 achieved SVR in 80% after 6 wk and SVR in 94% after 8 wk of treatment. In genotype 3 non-cirrhotic patients were treated for 8 and 12 wk resulting in SVR-rates of 93% and 100%.
Cirrhotic genotype 3 patients being treated only for 12 wk achieved a SVR-rate of 91% [46]. These future substances will enable a shortened treatment time and increase the antiviral activity in individual populations. A selection of future therapies and their phase II - III trial results are presented in Table 4 [46-53].

As of mid 2016, the 2nd generations DAAs are expected to be available. These therapy regimes will have pan-genotypic and high antiviral effectiveness as well as a better resistance profile. It is likely that R will become dispensable and treatment duration may decrease in individual populations. A higher proportion of infected patients would have to be treated. This will only be possible by an increased screening of risk populations and customized pricing.

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