Treatment of Chronic Hepatitis C: Efficacy, Side Effects and Complications

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Keywords

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Abstract

Background: Chronic hepatitis C virus (HCV) infection can lead to liver cirrhosis and its complications. Viral eradication is essential to prevent disease progression and reduces liver-related mortality and morbidity. Since the availability of direct-acting antivirals (DAA), HCV treatment has changed significantly. Current treatment strategies for different groups of patients as well as potential risks and caveats will be discussed in this review. **Summary:** Interferon-free (IFN-free) treatment not only shortens treatment duration, but also achieves high rates of viral clearance and is overall well tolerated. Genotype-restricted but also pangenotypic combinations are available. Usually two DAA of different drug classes are combined. For the majority of the patients, treatment duration ranges from 8 to 12 weeks. Liver and kidney function as well as prior treatment experience and potential drug-drug interactions influence substance choices and treatment duration. However, modern IFN-free treatment is not only safer, but also overall far more simplified and effective. Global HCV eradication might be an ambitious but not completely unrealistic goal to pursue. **Key Messages:** IFN-free antiviral treatment is safe and well tolerated. Patients can be treated almost independently of liver function or concomitant disease. Viral eradication is associated with reduced morbidity and mortality and better quality of life.

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Introduction

With approximately 71 million people infected worldwide, hepatitis C virus (HCV) infection is a major global health concern. Chronic infection can lead to liver cirrhosis, hepatic decompensation and/or hepatocellular carcinoma which are associated with high morbidity and mortality [1, 2]. In addition, HCV can be associated with relevant extrahepatic manifestations like hematoproliferative disorders and has recently been identified as a risk factor for cardiovascular diseases. The main objective of antiviral treatment is the reduction of these complications by achieving complete viral eradication defined as undetectable HCV RNA 12 weeks after the end of antiviral treatment (sustained virological response, SVR) [3]. Even in patients who already developed advanced liver fibrosis, a normal life expectancy can be achieved by viral eradication as it has been shown by data derived from interferon (IFN)-based therapies [4]. Of note, it has been shown that SVR not only reduces liver-related morbidity and mortality, but also improves health-related quality of life [5–8]. Since the availability of direct-acting antivirals (DAA), HCV therapy has been revolutionized. Compared to former IFN-based regimens DAA treatment is highly effective in the majority of the patients. Therapy is not only shorter, but also well tolerated and even most patients with former contraindications to IFN therapy, mainly patients with decompensated cirrhosis or significant comorbidities, can now be treated. Despite the overall success, antiviral treatment of certain groups of patients remains challenging. Even if severe side effects are

Fig. 1. The replication cycle of the hepatitis C virus and modes of action of direct-acting antivirals are displayed (adapted from Manns and Cornberg [69] and Mauss et al. [70]).

rare, they are not completely absent especially in patients with advanced liver disease in whom the usage of ribavirin (RBV) is still recommended [3, 9, 10]. Furthermore, the possibility of drug-drug interactions (DDI) is of special concern since nowadays patients with severer comorbidities might be treated due to overall good tolerability of DAA treatment [11–13]. And last but not least, a minority of patients fails DAA treatment and is in need of second-line antiviral therapy for which resistance-associated substitutes (RAS) may sometimes need to be considered.

In this review we will discuss the current antiviral treatment strategies and elucidate remaining challenges and caveats during DAA therapy.

Current Antiviral Treatment Strategies

The introduction of DAA revolutionized the field of antiviral therapy for patients chronically infected with HCV. Antiviral therapy usually consists of at least two antiviral substances from different drug classes with different modes of action (Fig. 1). Treatment decisions are based on (sub-)genotype (GT), presence of cirrhosis and

response to prior treatments [3]. Typical treatment regimens for patients with and without compensated cirrhosis are depicted in Tables 1 and 2. All different recommended regimens achieve SVR rates of more than 95% if administered correctly [3].

The pangenotypic drug combinations sofosbuvir/velpatasvir and glecaprevir/pibrentasvir show high antiviral efficacy against all HCV genotypes. Treatment duration differs from 8 weeks for glecaprevir/pibrentasvir in non-cirrhotic treatment-naïve patients to 12 weeks for patients with liver cirrhosis or 16 weeks for GT 3 patients with liver cirrhosis and/or prior treatment failure. Sofosbuvir/velpatasvir has to be administered for 12 weeks independently of fibrosis level [3]. Treatment with grazoprevir/elbasvir is possible in patients with GT 1 or 4 infection and has to be administered for 12–16 weeks depending on GT, fibrosis stage and viral load [3].

In most of the cases treatment is well tolerated, and the coadministration of RBV is not necessary. One exception are patients with decompensated liver cirrhosis. These patients benefit from RBV treatment, and higher SVR rates are achieved in particular in those infected with GT 3 [3, 14].

Table 1. Treatment of patients with chronic hepatitis C without cirrhosis (adapted from Pawlotsky et al. [3] and Mauss et al. [70])

GT	Pretreatment	SOF/LDV, weeks	GZR/ELB, weeks	GLE/PIB, weeks	SOF/VEL, weeks	SOF/VEL/VOX, weeks
1a	No (naïve)	8 ⁶	12 ²	8	12	8 ⁵
	IFN/RBV/SOF	12 ^{3,5}	12 ^{2,3}	8 ⁸	12 ³	8 ⁹ –12 ⁵
	DAA with NS5A inhibitor	No	No	16 ⁷	No	12
1b	No (naïve)	8 ⁶	12 ⁴	8	12	8 ⁵
	IFN/RBV/SOF	12 ³	12 ³	8 ⁸	12 ³	8 ⁹ –12 ⁵
	DAA with NS5A inhibitor	No	No	16 ⁷	No	12
2	No (naïve)	No	No	8	12	8 ⁵
	IFN/RBV/SOF	No	No	8	12	8 ⁹ –12 ⁵
	DAA with NS5A inhibitor	No	No	No	No	12
3	No (naïve)	No	No	8	12	8 ⁵
	IFN/RBV/SOF	No	No	16 ¹	12	8 ⁹ –12 ⁵
	DAA with NS5A inhibitor	No	No	No	No	12
4	No (naïve)	12	12 ²	8	12	8 ⁵
	IFN/RBV/SOF	12 ^{3,5}	12 ^{2,3,5}	8	12 ³	8 ⁹ –12 ⁵
	DAA with NS5A inhibitor	No	No	No	No	12
5, 6	No (naïve)	12	No	8	12	8 ⁵
	IFN/RBV/SOF	No	No	8	12	8 ⁹ –12 ⁵
	DAA with NS5A inhibitor	No	No	No	No	12

ELB, elbasvir; GLE, glecaprevir; GZR, grazoprevir; LDV, ledipasvir; IFN, pegylated interferon- α ; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir; DAA, direct-acting antiviral. ¹ EASL recommends 12 weeks. ² HCV-RNA <800,000 IU/mL at baseline and exclusion of NS5A RAS. ³ Including treatment experience with IFN + RBV + protease inhibitor (simeprevir, telaprevir or boceprevir). ⁴ 8 weeks if F0–F2 fibrosis stage. ⁵ Not recommended by EASL. ⁶ Patients with HCV-RNA <6 million IU/mL at baseline. ⁷ Prior therapy with NS5A inhibitor but without protease inhibitor (FDA label, not recommended by EMA). ⁸ 12 weeks if pretreatment with protease inhibitor but without NS5A inhibitor (FDA label, not recommended by EMA). ⁹ DAA-naïve patients.

Table 2. Treatment of patients with chronic hepatitis C with compensated cirrhosis (adapted from Pawlotsky et al. [3] and Mauss et al. [70])

GT	Pretreatment	SOF/LDV, weeks	GZR/ELB, weeks	GLE/PIB, weeks	SOF/VEL, weeks	SOF/VEL/VOX, weeks
1a	No (naïve)	12 ⁵	12 ¹	12	12	12 ³
	IFN/RBV/SOF	12 ^{3,5}	12 ^{1,2}	12 ⁷	12 ²	12 ³
	DAA with NS5A inhibitor	No	No	16 ⁶	No	12
1b	No (naïve)	12 ⁵	12	12	12	12 ³
	IFN/RBV/SOF	12 ⁵	12 ²	12 ⁷	12 ²	12 ³
	DAA with NS5A inhibitor	No	No	16 ⁶	No	12
2	No (naïve)	No	No	12	12	12 ³
	IFN/RBV/SOF	No	No	12	12	12 ³
	DAA with NS5A inhibitor	No	No	No	No	12
3	No (naïve)	No	No	12	12 ^{3,4}	8 ⁸
	IFN/RBV/SOF	No	No	16	12 ^{3,4}	12
	DAA with NS5A inhibitor	No	No	No	No	12
4	No (naïve)	12	12 ¹	12	12	12 ³
	IFN/RBV/SOF	12 ^{3,5}	12 ^{1,2,3}	12	12 ²	12 ³
	DAA with NS5A inhibitor	No	No	No	No	12
5,6	No (naïve)	12	No	12	12	12 ³
	IFN/RBV/SOF	No	No	12	12	12 ³
	DAA with NS5A inhibitor	No	No	No	No	12

ELB, elbasvir; GLE, glecaprevir; GZR, grazoprevir; LDV, ledipasvir; IFN, pegylated interferon- α ; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir. ¹ HCV-RNA $\leq$ 800,000 IU/mL at baseline and exclusion of NS5A RAS. ² Including treatment experience with IFN + RBV + protease inhibitor (simeprevir, telaprevir or boceprevir). ³ Not recommended by EASL. ⁴ If NS5A RAS (Y93H) detected additional RBV recommended. ⁵ If platelets <75,000/ μ L RBV should be added or/and treatment may be extended to 24 weeks. ⁶ Prior therapy with NS5A inhibitor but without protease inhibitor (FDA label, not recommended by EMA). ⁷ Pretreatment with protease inhibitor but without NS5A inhibitor (FDA label, not recommended by EMA). ⁸ EASL recommends 12 weeks.

Special Groups of Patients

Treatment of Patients with Prior DAA Treatment Failure

After failure of DAA treatment, the development of RAS is very likely. RAS linked to the NS5A gene are more likely to persist for a longer time at a significant level than those connected to the NS3/4 gene. RAS relevant for the NS5B inhibitor sofosbuvir are usually rapidly suppressed after treatment cessation due to a significantly impaired viral fitness. Resistance testing and the adaptation of antiviral regimes according to RAS is one possible option for retreatment [15, 16]. Currently, the only approved drug combination for the retreatment of patients with prior DAA failure is the combination of sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) [3]. This combination is not only well tolerated, but also highly effective, and SVR rates >95% can be achieved in pretreated patients independently from the initial treatment regimen [17]. The recommended treatment duration for DAA-experienced patients is 12 weeks [3, 18]. Preliminary real-world data confirmed the high efficacy of the SOF/VEL/VOX in previous DAA failures. All of the first 110 patients who had completed SOF/VEL/VOX in the German Hepatitis C Registry achieved SVR [19]. Excellent results have also been reported from French and US cohorts [20, 21]. Due to its effectiveness this combination should be reserved for the retreatment of patients with prior DAA failure and is usually not recommended for the initial treatment of therapy-naïve patients [18].

However, not all patients with failure of a first DAA therapy have to be treated with SOF/VEL/VOX. Patients with GT 1 infection and previous antiviral treatment that only included a first-generation protease inhibitor are well eligible for treatment with sofosbuvir/ledipasvir, grazoprevir/elbasvir or sofosbuvir/velpatasvir. Furthermore, the retreatment with glecaprevir/pibrentasvir for 12 or 16 weeks (patients with liver cirrhosis) is possible but currently not approved by the EMA label [22]. Finally, the “off-label” combination of sofosbuvir, glecaprevir/pibrentasvir and RBV was evaluated in the MAGELLAN-3 study for patients who failed prior therapy with glecaprevir/pibrentasvir [23]. Only 1 patient of 23 experienced viral relapse after 12 or 16 weeks of treatment.

Treatment of Patients with Impaired Renal Function/Dialysis

Renal excretion is the main elimination pathway of the NS5B polymerase inhibitor sofosbuvir and its metabolites. For patients with mild to moderate renal impairment administration of sofosbuvir is safe. Since patients with severe renal dysfunction or hemodialysis have not been included during the initial phase III study trials, drug safety of sofosbuvir in these patients has not been studied in

detail, and therefore sofosbuvir treatment is not recommended by the FDA and EMA label. Nevertheless, some real-world studies and preliminary data of a prospective multicenter trial show high efficacy and safety during full dose sofosbuvir treatment for patients with severe kidney dysfunction-related discontinuations or treatment-related serious adverse events [24–26]. However, in some studies these patients also experience higher rates of anemia and worsening of kidney dysfunction [27]. Therefore, sofosbuvir-free treatment options should be preferred if possible. Since the introduction of the pangenotypic combination of glecaprevir/pibrentasvir, a highly effective treatment of GT 2 and 3 is available, and safety and efficacy for patients with renal impairment and hemodialysis have been shown successfully [28]. Alternatively, grazoprevir/elbasvir can be safely administered in patients with GT 1 or 4 infection and severe renal dysfunction [29].

Treatment of Patients with Decompensated Cirrhosis

Treatment of patients with decompensated cirrhosis (Child-Pugh Score B/C (CPS B/C)) is limited to regimens containing sofosbuvir and NS5A inhibitors. Protease inhibitors are not recommended due to the hepatic metabolism and subsequently significantly higher drug exposure in this group of patients. Thus, grazoprevir/elbasvir, glecaprevir/pibrentasvir or SOF/VEL/VOX should not be administered. To improve efficacy the remaining combination of sofosbuvir and NS5A inhibitor should be combined with RBV [3]. Many studies and real-world data have shown that IFN-free antiviral therapy is safe in patients with advanced liver disease. However, patients are still at risk of hospitalization during therapy, mainly because of complications from liver disease [30–32]. The efficacy of sofosbuvir/ledipasvir plus RBV was studied in the SOLAR-1 and -2 study. In GT 1 patients, SVR rates ranged between 87 and 96% and between 72 and 85% in CPS B and CPS C patients, respectively [31, 33]. The ASTRAL-4 study evaluated the use of sofosbuvir/velpatasvir in patients with CPS B, but not CPS C. Treatment duration of 12 weeks showed high rates of SVR for patients with GT 1, 2, 4 and 6 infection. SVR rates of GT 3 were low at 50% but could be increased to 85% by the addition of RBV [14]. Even though the rate of treatment discontinuations is higher in patients treated with RBV, the additional antiviral substance significantly increases SVR rates [3].

Patients with not only decompensated liver cirrhosis, but also additional kidney dysfunction, prior DAA treatment failure or GT 3 infection are especially difficult to treat and should be referred to specialized centers since the administration of sofosbuvir has not been extensively studied in these groups of patients. Similarly, antiviral treatment in patients awaiting liver transplantation should be discussed with the responsible transplantation

unit. Advantages of viral eradication with improvement of liver function and the prevention of reinfection of the graft have to be outweighed against potential risks of antiviral treatment in patients with decompensated cirrhosis [34]. Generally antiviral treatment after liver transplantation is safe and effective and could also be deferred to the post-transplantation setting. The current IDSA/AASLD guideline recommends treatment prior to liver transplantation in individuals with a MELD (model of end-stage liver disease) up to 20, while the current EASL guideline is slightly more conservative suggesting a cutoff at 18–20 MELD points [3, 18].

Basically, feasibility of antiviral treatment in liver transplantation candidates should be discussed with the responsible transplantation unit based on the individual health status of the patient and local chances of transplantation.

DAA Treatment and Hepatocellular Carcinoma

The impact of DAA treatment on hepatocellular carcinoma (HCC) incidence, recurrence and tumor aggressiveness in patients with chronic HCV infection has been intensively discussed over the last 2 years. Shortly after DAA approval, an observed increase in early occurrence or recurrence of HCC after HCV eradication with DAA has been reported [35, 36].

However, the higher incidence of de novo HCC compared to historical data was most likely related to a significantly higher proportion of older patients as well as those with end-stage liver disease certainly ineligible for IFN-based regimens. Later on, further data analysis revealed that HCV eradication due to DAA treatment reduces the risk of HCC development to a comparable level as with IFN-based therapies [37]. These findings were supported by results from prospective studies showing a reduction of HCC incidence in patients with HCV-related liver cirrhosis [38]. Nevertheless, the absolute risk of HCC development remains high in patients with established cirrhosis. Ongoing HCC surveillance is mandatory despite HCV clearance [39].

In contrast, the impact of DAA treatment on HCC recurrence might be more controversial [40]. However, it has to be noted that the majority of HCC recurrences during DAA therapy occurred within the first 6 months after HCC treatment. Furthermore, according to a retrospective study from North America and a prospective study from Italy, HCC recurrence rates were similar between DAA and non-DAA treatment in patients with liver cirrhosis and curative oncological treatment prior to antiviral treatment. Patients treated with DAA showed improved overall survival and a reduced risk of hepatic decompensation [41, 42]. In our opinion, patients with HCV cirrhosis who have undergone definite HCC treatment with confirmed success 6 months after should not

be excluded from DAA treatment to prevent the progression of liver disease.

Treatment after Liver Transplantation

After liver transplantation reinfection of the graft leads to fast development of liver fibrosis, and consequently the risks of organ dysfunction and graft loss are significantly increased [43, 44]. Thus, antiviral treatment is essential to preserve liver function and ensure transplant survival [45]. Severe post-transplantation cholestatic hepatitis and patients with moderate to severe fibrosis need urgent initiation of antiviral treatment to prevent graft loss [44, 46]. In the SOLAR-1 and -2 trials patients after liver transplantation show similar SVR rates compared to nontransplanted patients with the treatment of sofosbuvir/ledipasvir plus RBV [31, 33]. Comparable results were achieved by the combination of sofosbuvir/velpatasvir [47]. These results are supported by data from several real-world studies confirming the efficacy and safety of DAA treatment in the post-transplantation setting. Potential DDI between DAA and immunosuppressive drugs require special attention, in particular when using protease inhibitors. However, the combination of glecaprevir/pibrentasvir is certainly a valuable pangenotypic alternative to sofosbuvir-containing regimens, in particular for patients with impaired kidney function after liver transplantation [48]. During DAA treatment serum levels of immunosuppressant drugs have to be closely monitored.

Treatment of Patients with Co-Infection

In patients with hepatitis B virus (HBV) co-infection, HBV DNA is usually low although fluctuation cannot be excluded whereas HCV RNA is present and the driver of hepatic inflammation. Before antiviral treatment the replicative virus status including hepatitis delta has to be determined. In case of present HCV RNA, antiviral treatment against HCV should be initiated following the same recommendations as for monoinfected patients [3]. SVR rates of HCV therapy are not impaired by HBV co-infection or HBV treatment and, although tenofovir displays potential DDI with DAA, the administration of entecavir is uncomplicated [49, 50]. Some studies report an increase in HBV DNA levels or HBV reactivation during HCV antiviral treatment but so far, the risk of reactivation and possible clinical deterioration are unpredictable [51–53]. Current guidelines recommend initiation of concomitant antiviral HBV treatment in patients with positive HBs antigen. In case of negative HBs antigen but anti-HBc-positive antibodies, alanine transaminase (ALT) levels should be monitored irrelevant of anti-HBs antibody status. If ALT levels do not normalize or rise during DAA therapy and HBs antigen or HBV DNA are detectable, HBV treatment should be initiated [3].

Table 3. Induction and inhibition of enzymes or transporters by active substances for HCV therapy

	↑ Induction / inhibition ↓ (details)			
	CYP	P-gp	OATP	BCRP
Daclatasvir	↑ (3A4, weak)	↓ (cave: narrow TR)	↓ (1B1)	↓
Simeprevir	↓ (1A2, intestinal 3A4; both weak)	↓	↓ (1B1/3)	↓
Sofosbuvir	no interaction expected	no interaction expected	no interaction expected	no interaction expected
Ribavirin	no interaction expected	no interaction expected	no interaction expected	no interaction expected
SOF/LDV	no interaction expected	↓ (in vitro)	↓ (possible)	↓ (in vitro)
GZR/ELB	↓ (3A, weak, in vivo)	↓ (weak, intestinal, in vivo)	no interaction expected	↓ (intestinal)
GLE/PIB	↓ (3A, weak, in vivo)	↓	↓ (1B1/3)	↓
SOF/VEL	no interaction expected	↓ (in vitro)	↓ (1B, in vitro)	↓ (in vitro)
SOF/VEL/VOX	no interaction expected	↓ (in vitro)	↓ (1B, in vitro)	↓ (in vitro)
Substrates	1A2: theophylline 3A4: cyclosporine	dabigatran, digoxin, carvedilol	1B: simvastatin, atorvastatin	simvastatin, atorvastatin

SOF, sofosbuvir; LDV, ledipasvir; GZR, grazoprevir; ELB, elbasvir; GLE, glecaprevir; PIB, pibrentasvir; VEL, velpatasvir; VOX, voxilaprevir; CYP, cytochrome P-450 enzyme; P-gp, permeability glycoprotein; OATP, organic anion-transporting polypeptide; BCRP, breast cancer resistance protein; TR, therapeutic range.

Treatment recommendations for patients with HCV/HIV co-infection do not differ from HCV-monoinfected patients. Potential DDI between antiretroviral drugs and DAA have to be taken into account before choosing a DAA regimen, especially if NS3/4 protease inhibitors are included [3, 18].

Side Effects

Former antiviral regimens containing protease inhibitors like boceprevir or telaprevir combined with peginterferon alfa had serious side effects [54, 55]. When looking at more modern regimens like glecaprevir/pibrentasvir, elbasvir/grazoprevir and velpatasvir/sofosbuvir ± voxilaprevir, the potential for side effects does not seem to turn the balance in HCV therapy anymore. All substances are mostly well tolerated. The most important side effects are headache, fatigue, nausea and diarrhea and occur in $\geq 1/10$ patients. Additionally, the possible increases in ALT levels and bilirubin are important and need to be monitored during therapy. Anyhow less than 1% of patients have to discontinue therapy due to side effects [56–59]. Ribavirin, still being a treatment option in some cases, causes hemolytic anemia in $\geq 1/10$ patients [60]. This can result in dose reductions or even discontinuation of RBV treatment. When using RBV in HCV/HIV co-infected patients, a possible mitochondrial toxicity and lactate acidosis need

to be kept in mind. Due to the fact that records of possible side effects of RBV were often conducted in combination with peginterferon, interpretation as RBV specific side effects should always be made with caution [61].

DDI as Complication in HCV Therapy

On the one hand side effects, not being a major issue in HCV therapy anymore, are a disappearing challenge. On the other hand, DDI have expanded as a new complication when treating with DAA. Several publications over the last few years have pointed out that up to 40% of HCV patients might be affected by significant DDI [13, 62]. DDI can either have pharmacodynamic or pharmacokinetic impact or both on all involved substances. Table 3 summarizes pharmacokinetic information about the active substances for HCV treatment according to the prescribing information (as of May 2019). The classical substrates mentioned in Table 3 are kinetically influenced by concomitant use of DAA, and the risk of adverse events like dose-dependent toxicity, higher bleeding risk, adverse cardiac events or rhabdomyolysis increases. On the basis of these data a prediction of possible DDI can be made. Not only substances for HCV treatment can influence the kinetics of other drugs, this can also occur vice versa. For example, metformin is a CYP 3A4 inducer and may decrease concentrations of DAA being metabolized via this enzyme [50].

Table 4. Drug-drug interactions and clinical management

ATC code	Active pharmaceutical ingredient	Sofosbuvir + ledipasvir	Grazoprevir + elbasvir	Glecaprevir + pibrentasvir	Sofosbuvir + velpatasvir	Sofosbuvir + velpatasvir + voxilaprevir
A02BC	Pantoprazole, omeprazole, esomeprazole	Max. 20 mg omeprazole per day, do not take before DAA intake	No management required	Max. 40 mg omeprazole per day	Max. 20 mg omeprazole per day, 4 h after DAA, take DAA before a meal	Max. 20 mg omeprazole per day
C09CA	Candesartan	No management required	Monitor ALT levels	Monitor ALT levels	No management required	Monitor ALT levels
N02BB	Metamizole	No management required	(1) Stop metamizole treatment (2) Use ibuprofen or paracetamol (3) Continue metamizole treatment and monitor response for HCV treatment	(1) Stop metamizole treatment (2) Use ibuprofen or paracetamol (3) Continue metamizole treatment and monitor response for HCV treatment	(1) Stop metamizole treatment (2) Use ibuprofen or paracetamol (3) Continue metamizole treatment and monitor response for HCV treatment	(1) Stop metamizole treatment (2) Use ibuprofen or paracetamol (3) Continue metamizole treatment and monitor response for HCV treatment
C10AA	Simvastatin	Use simvastatin in lowest possible dose and monitor	Max. 20 mg simvastatin per day	(1) Stop simvastatin treatment (2) Use pravastatin (max. 20 mg per day) or rosuvastatin (max. 5 mg per day)	(1) Use simvastatin with caution and in reduced dose (2) Use pravastatin instead (no dose adjustment)	(1) Stop simvastatin treatment (2) Use pravastatin (max. 40 mg per day) (3) Use simvastatin in lowest possible dose and monitor
C07AG	Carvedilol	Close monitoring for possible carvedilol intoxication	No management required	Close monitoring for possible carvedilol intoxication	Close monitoring for possible carvedilol intoxication	Close monitoring for possible carvedilol intoxication
A02AH	Sodium hydrogen carbonate	(1) Use drug formulation with no impact on gastric pH value (2) Stop treatment for period of DAA therapy	No management required	(1) Use drug formulation with no impact on gastric pH value (2) Stop treatment for period of DAA therapy	(1) Use drug formulation with no impact on gastric pH value (2) Stop treatment for period of DAA therapy	(1) Use drug formulation with no impact on gastric pH value (2) Stop treatment for period of DAA therapy
B01AA	Phenprocoumon	Monitor INR levels	Monitor INR levels	Monitor INR levels	Monitor INR levels	Monitor INR levels
L04AD	Cyclosporine	No management required	Stop cyclosporine treatment and evaluate alternative options for immunosuppression during DAA therapy	(1) Coadministration not recommended when used with >100 mg cyclosporine per day (2) If necessary only with positive risk-benefit ratio and under monitoring	No management required	Stop cyclosporine treatment and evaluate alternative options for immunosuppression during DAA therapy
C01BD	Amiodarone	Stop amiodarone treatment and evaluate alternative therapy options (cave: due to long half-life of amiodarone, monitoring for several months after discontinuation still needed)	Close monitoring (drug levels, ECG and adverse events) for possible amiodarone intoxication	Close monitoring (drug levels, ECG and adverse events) for possible amiodarone intoxication	Stop amiodarone treatment and evaluate alternative therapy options (cave: due to long half-life of amiodarone, monitoring for several months after discontinuation still needed)	Stop amiodarone treatment and evaluate alternative therapy options (cave: due to long half-life of amiodarone, monitoring for several months after discontinuation still needed)
C01AA	Digoxin	Use digoxin with caution and monitor digoxin blood levels	No management required	Use digoxin with caution and monitor digoxin blood levels	Use digoxin with caution and monitor digoxin blood levels	Use digoxin with caution and monitor digoxin blood levels
B01A (E-F)	Dabigatran, rivaroxaban, edoxaban	(1) Use combination with caution and closely monitor for bleeding and anemia (2) Consider low-molecular heparin as alternative treatment option	(1) Use combination with caution and closely monitor for bleeding and anemia (2) Consider low-molecular heparin as alternative treatment option	(1) Stop dabigatran treatment (2) Use rivaroxaban and edoxaban with caution and closely monitor for bleeding and anemia (3) Also consider edoxaban dose reduction after risk-benefit analysis 4) Consider low-molecular heparin as alternative treatment option	(1) Use combination with caution and closely monitor for bleeding and anemia (2) Consider low-molecular heparin as alternative treatment option	(1) Stop dabigatran and edoxaban treatment (2) Use rivaroxaban or apixaban with caution and closely monitor for bleeding and anemia (3) Consider low-molecular heparin as alternative treatment option

ATC code, a anatomical therapeutic chemical classification code; max., maximum; DAA, direct-acting antiviral; ALT, alanine aminotransferase; HCV, hepatitis C virus; INR, international normalized ratio; ECG, electrocardiography.

Looking at proton pump inhibitors the increasing pH value in the stomach under therapy leads to decreased solubility of ledipasvir, glecaprevir and velpatasvir. This causes lower bioavailability and potentially even a higher risk of efficacy loss. The clinical relevance of this interaction seems to be dose dependent [50, 56, 63]. Candesartan is a permeability glycoprotein inhibitor, and concentrations of DAA transported via permeability glycoprotein may be increased. In case of dose dependent ALT elevations closer monitoring may be required [50]. A possible fluctuation of liver function during and after therapy of HCV patients can cause a change of INR levels when under anticoagulative therapy with phenprocoumon. Patients should be closely monitored during concomitant use [50, 56–59]. The combination of ethinylestradiol with glecaprevir/pibrentasvir and velpatasvir/sofosbuvir + voxilaprevir can lead to ALT elevation and is therefore contraindicated [56, 59]. Last but not least DDI with the following medications need also to be kept in mind when treating with DAA: (1) amiodarone, (2) St. John's wort, (3) rifampicin, (4) anti-epileptic drugs, (5) antiretroviral medications and (6) psychotropic drugs [50, 64, 65].

However, theoretical potential for interactions does not always result in clinically relevant DDI. When predicting clinically relevant DDI, the following point needs to be kept in mind. DDI studies with reliable clinical end points or pharmacokinetic data are most eligible to determine clinical significance but still need an expert for interpretation, and in most cases such studies are not available [66]. Table 4 shows commonly used concomitant medications in HCV, clinically relevant DDI with modern HCV regimens and the suggested management based on prescription information (as of May 2019), www.hep-druginteractions.org (as of May 2019) and authors' expertise [67].

Conclusion and Remaining Challenges

With the availability of DAA, high rates of viral eradication can be realized while treatment is overall safe. DDI need to be considered but are well manageable. Given that

antiviral treatment is highly effective, treatment accessibility seems to be the current limitation of HCV eradication. Screening of patients has to be improved for the identification of infected patients prior to the development of liver disease. Especially in high-risk populations (intravenous drug users, prison inmates, men who have sex with men), infected patients have to be identified and importantly need to be treated to limit viral spreading. Therefore, barriers to treatment access like e.g. treatment pricing or medical infrastructure have to be addressed to allow treatment of the “unreached” patients [68]. To ensure the sustainability of antiviral treatment, prevention activities have to be implemented and improved and might even include the development of an HCV vaccine which is not available yet.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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