Chapter 7

Direct-Acting Antivirals (DAAs): Drug-Drug Interactions (DDIs) in the Treatment of Hepatitis C Virus (HCV)

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Additional information is available at the end of the chapter

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Abstract

Hepatitis C virus (HCV)-infected patients often use multiple medications to treat infection, adverse events related to HCV therapy, or to manage other comorbidities. Drug-drug interactions (DDIs) associated with this polypharmacy are important in HCV pharmacotherapy, especially after introduction of direct-acting antivirals (DAAs). Knowledge about pharmacokinetics, metabolism, and disposition of drugs used in the treatment of HCV and comorbidities is crucial in the interpretation of these data and management of these interactions (e.g. dose adjustments, therapeutic drug monitoring, or safe alternatives). Web-based DDIs interactive tools like http://www.hep-druginteractions.org represent the most feasible and comprehensive way for an assessment of potential DDIs before, during, and after treatment. Additional helpful resources are data from clinical drug interaction studies as well as recent real-life data. This chapter is practical overview of DDIs in the treatment of HCV with the last update.

Keywords: hepatitis C virus, direct-acting antivirals, drug-drug interactions, cytochrome P450, antiviral therapy

1. Introduction

Hepatitis C virus (HCV) is one of the leading causes of liver disease in the world [1, 2]. HCV can cause acute and chronic infections. Acute infection is a non-life threatening disease and ranges from being asymptomatic to causing a self-limited hepatitis. Acute HCV infection is usually asymptomatic and is only very rarely associated with life-threatening disease. About 15–45% of acutely infected patients spontaneously clear HCV within several months after infection, but the remaining 55–85% of patients develop chronic infection [3, 4]. Currently, almost 180 million people in the world have chronic HCV infection [2, 3]. The risk of cirrhosis

of the liver is between 15 and 30% within 20 years for patients with chronic HCV infection, and the risk of hepatocellular carcinoma increases (HCC) more than 20-fold within 20 years of infection. Approximately, 700,000 persons die each year from HCV-related complications, which include cirrhosis, hepatocellular carcinoma (HCC), and liver failure [4].

The goal of therapy is to cure HCV infection in order to prevent the complications of HCV-related liver and extrahepatic diseases, such as fibrosis, cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations, and death [4]. The gold standard of therapy for the treatment of chronic HCV infection for many years was pegylated interferon (Peg-INF) in combination with ribavirin (RBV). Over the past decade, the treatment of hepatitis C has dramatically improved. Limited efficacy in patients with HCV and side effects of indirect drugs, Peg-INF + RBV spurred the development of new therapeutic approaches. Almost 80 percent of patients receiving Peg-INF + RBV combination therapy for chronic HCV infection had side effects. The appropriate anticipation and prevention of side effects, proper response when they occur, as well as recognition of patients at increased risk for side effects have pivotal role in the care of patients with chronic HCV infection. Furthermore, the ability to achieve a sustained virologic response (SVR) to therapy depends in part upon the degree of compliance with therapy. Reduction of the dose of these agents as well as their discontinuation due to side effects could potentially compromise the outcome.

Peg-INF can cause in many cases bone marrow depression with decreased granulocytes, which can lead to opportunistic infections and decreased numbers of thrombocytes [5]. Neutropenia is one of the most common reasons for dose modification. Flu-like symptoms usually occur during the first week of treatment and include chills, headaches, myalgia, and fever. Severe fatigue, apathy, and irritability are neuropsychiatric side effects, which are great problem for patients and their families. They can even lead to suicide if they are not recognized on time [5]. A variety of autoimmune diseases can develop or be exacerbated during peginterferon-containing therapy, including psoriasis, vitiligo, rheumatoid arthritis, lichen planus, sarcoidosis, dermatitis herpetiformis, and type 1 diabetes mellitus [5]. Thus, peginterferon should be used with caution in patients with known autoimmune disease and is contraindicated in patients with known autoimmune hepatitis. The development of thyroid dysfunction is common in patients treated with peginterferon. On the other hand, most common side effect of RBV is hemolytic anemia. It may be necessary to lower the dose or even discontinue the therapy. In those cases, treatment with erythropoietin can reverse ribavirin-associated anemia and permit continuation of the RBV therapy [5]. The above-mentioned side effects, decreased adherence to therapy, prolonged treatment time as well as increased cost of HCV treatment are all hurdles to successful treatment.

2. Direct-acting antivirals (DAAs)

Before 2011, the gold standard of therapy was based on the combination of Peg-IFN and RBV that acts by mechanisms not completely known and exhibited low efficacy in most populations. In the recent years, thanks to basic research on HCV structure and replicative cycle, it has been possible to develop DAAs that have dramatically increased the viral clearance rates.

Specifically, the advent of the combined therapy employing DAAs has dramatically increased the viral clearance rate from 40–50% with peginterferon + ribavirin to more than 95% with the current therapy [3, 6]. Initially, DAAs for treatments of chronic HCV were more efficacious, but had even more side effects at beginning due to combined therapy PEG INF + ribavirin + DAAs (protease inhibitor) (PI). Some of the side effects of combination Peg INF + RBV+ PI inhibitors appeared due to drug-drug interactions. The first generation of NS3/4APIs (boceprevir and telaprevir) was approved for clinical use in 2011. Since then, the new standard in the treatment of chronic HCV infection became triple therapy consisting PEG INF/RBV and either boceprevir (BOC) or telaprevir (TVP). With the addition of boceprevir or telaprevir to PEG-IFN/RBV, cure rates for HCV genotype 1 increased to 60–70%. However, new protease inhibitors (PI)-containing triple therapy were also accompanied by new problems, including more complicated dosing regimens and increased adverse events, which were in some cases severe, particularly in patients with advanced liver disease. Furthermore, DDIs became additional challenges in HCV therapy. The first DAAs are metabolized by CYP3A4 and used transporter P-glycoprotein (P-gp) system. As a result, there is potential risk for DDIs with other drugs often used in the treatment of HCV patients. By 2013, the second generation of DAAs, including sofosbuvir, was introduced in the market.

Direct-acting antivirals target three of the main proteins involved in viral replication: the NS3/4A protease, the NS5B polymerase, and the NS5A [7].

2.1. NS3/4A protease inhibitors

NS3/4A protease inhibitors are inhibitors of the NS3/4A serine protease, an enzyme involved in post-translational processing and replication of HCV. Protease inhibitors disrupt HCV by blocking the NS3 catalytic site or the NS3/NS4A interaction. In addition to its role in viral processing, the NS3/NS4A protease blocks TRIF-mediated Toll-like receptor signaling and Cardif-mediated retinoic acid–inducible gene 1 (RIG-1) signaling, which result in impaired induction of interferons and blocking viral elimination. Thus, inhibition of the NS3/4A protease could contribute to antiviral activity through two mechanisms [7].

Following the introduction of other potent and better tolerated DAAs, the clinical importance of these agents diminished substantially because of their cumbersome administration, substantial adverse effects, drug-drug interactions, and low barrier to resistance. The subsequent wave of the first generation protease inhibitors (simeprevir, paritaprevir) as well as second generation (grazoprevir) offered several benefits over earlier protease inhibitors, including fewer drug-drug interactions, improved dosing schedules, and less frequent and less severe side effects. In addition, the newer protease inhibitors also appear to have increased efficacy against genotype 1 HCV and other genotypes. Grazoprevir, paritaprevir, and simeprevir are protease inhibitors available in the Europe and United States. Asunaprevir is a protease inhibitor used in Japan [7].

2.2. NS5A inhibitors

The NS5A protein plays a role in both viral replication and the assembly of the hepatitis C virus (HCV) [7]. However, the precise molecular mechanisms by which NS5A accomplishes these functions are unclear. NS5A inhibitors are generally quite potent and effective across all

genotypes. However, they have a low barrier to resistance and have variable toxicity profiles (**Table 1**). They have been shown to significantly reduce HCV RNA levels and enhance SVR when given in conjunction with peginterferon and ribavirin [18]. They also result in very high SVR rates among patients with genotype 1 infection when given in combination with other DAAs with or without ribavirin [8].

Available NS5A inhibitors are ledipasvir, ombitasvir, velpatasvir, and elbasvir, each available in fixed-dose combinations with other direct-acting antivirals, and daclatasvir. Daclatasvir is a NS5A inhibitor that is used mainly in combination with sofosbuvir [7].

2.3. NS5B RNA-dependent RNA polymerase inhibitors

NS5B RNA-dependent RNA polymerase is an enzyme necessary for replication of HCV, involved in post-translational processing of HCV and has a catalytic site for nucleoside binding and at least four other sites at which a non-nucleoside compound can bind and cause allosteric alteration. The enzyme's structure is highly conserved across all HCV genotypes, giving agents that inhibit NS5B efficacy against all six genotypes [7]. There are two classes of polymerase inhibitors: non-nucleoside analogues (NNPIs) and nucleoside/nucleotide analogues (NPIs). The NNPIs act as allosteric inhibitors, whereas NPIs target the catalytic site of NS5B and result in chain termination during RNA replication of the viral genome.

Sofosbuvir was the first NS5B NPIs available in the Europe and United States and can be used in various combinations with other antivirals for different indications.

As a class, NNPIs are less potent, more genotype specific (optimized for genotype 1), have a low-to-moderate barriers to resistance and have variable toxicity profiles [7]. Consequently, this class of drug was developed primarily as an adjunct to more potent compounds with higher barriers to resistance. Dasabuvir is administered and packaged with ombitasvir-paritaprevir-ritonavir.

Also, "the second generation" PIs, simeprevir, resulted in similar SVR rates when added to PEG-IFN/RBV. By 2014, IFN-free regimens had essentially replaced interferon-based therapy. Sofosbuvir/ledipasvir and sofosbuvir/simeprevir/RBV resulted in genotype 1 SVR rates of 92–100%. Combination of ombitasvir, paritaprevir/ritonavir/dasabuvir with/without RBV achieved SVR rates as high as 100%. The next step in the clinical development of anti-HCV therapy was by 2016 with the availability of pangenotypic ultrarapid (4–8 weeks) single pill regimens such as grazoprevir/elbasvir. This review is focused on drug-drug interactions in the treatment of HCV infections in past several years.

3. Metabolic pathways of DAAs

Most of the interactions are linked to metabolism of cytochrome P450-3 A4 (CYP3A4) or hepatic and/or intestinal transporters such as organic anion-transporting polypeptide (OATP) and P-glycoprotein (P-gp) as shown in **Table 1** [8]. To a lesser extent, other pathways can be involved such as breast cancer resistance protein transporter (BCRP) or multi-drug resistance protein 2 (MDRP2).

Direct antiviral agents (DAAs)	Metabolism	Transporter	Clinical DDI extent	Year of approval/ withdrawal	Drug in combination with	Brand name	Comment
Protease inhibitors-previrs							
Boceprevir	AKR, CYP3A4	P-gp BCRP	High	2011/2014	Not applicable	Victrelis	No longer available
Telaprevir	CYP3A4	P-gp, OATP1B1 OATP2B1	High	2011/2014	Not applicable	Incivo	No longer available
Simeprevir	CYP3A4	P-gp OATP1B1/3 OATP2B1	Moderate	2013	Sofosbuvir	Olysio	Approved as combination with sofosbuvir in 2014
Paritaprevir	CYP3A4	P-gp, BCRP OATP1B1/3	Height	2014 2015 2016	Ombitasvir, dasabuvir, ribavirin Ombitasvir, ribavirin Ombitasvir, dasabuvir, ribavirin	Viekira Pak (Technivie) Viekira XR	
Grazoprevir	CYP3A4	P-gp, MDRP2, OATP1B1	Low	2016	In combination with elbasvir	Zepatier	
NS5A inhibitors-buvirs							
Non-nucleoside inhibitors							
Sofosbuvir	Cathepsin A, esterases and kinases	P-gp and BCRP	Low	20132014	Ledipasvir	Sovaldi Harvoni	First treatment without interferon or ribavirin
Non-nucleoside inhibitors							
Dasabuvir			High	20142016	Ombitasvir, paritaprevir, and ribavirin	Viekira PakViekira XR	
NS5A inhibitors-asvirs							

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Direct antiviral agents (DAAs)	Metabolism	Transporter	Clinical DDI extent	Year of approval/ withdrawal	Drug in combination with	Brand name	Comment
Ombitasvir	CYP 3A4	P-gp, BCRP	High	20142016	Paritaprevir, dasabuvir, and ribavirin	Viekira Pak Viekira XR	
Ledipasvir			Low	2014	Sofosbuvir	Harvoni	
Daclatasvir	CYP3A4	P-gp,BCRP, OATP1B1, OATP1B3	Low	2015		Daklinza	
Elbasvir	CYP3A4	P-gp and BCRP	Low	2016	Grazoprevir	Zepatier	To treat GT1–4 including compensated cirrhosis, or severe kidney disease and on dialysis
Velpatasvir	CYP3A4	Inhibits OATP1B1, OATP1B3, OATP2B1, P-gp, BCRP	Low	2016	Sofosbuvir	Epclusa	First therapy to treat all HCV GT 1–6

Adapted according to [8–10].

Table 1. DAAs, metabolism, transporters, potential for DDI, and some basics.

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The good understanding of pharmacokinetic drug profiles is the key to interpret DDIs data. DDIs are more likely to occur with 3D regimen, followed by daclatasvir, simeprevir, and ledipasvir, as they are all both substrates and inhibitors of P-gp and/or CYP3A4, than with sofosbuvir [8–10]. Their concentrations may be influenced by CYP3A4 and P-gp inducers or inhibitors or they can increase concentrations of coadminstered drugs. Low dose or overdosage can be expected with potent inducers or inhibitors of drugs with narrow therapeutic range [8–10].

4. Drug-drug interactions with DAAs

Direct antiviral agents (DAAs) improved tolerability and efficacy for HCV-infected patients, but drug-drug interactions (DDIs) have the potential to cause harm due to liver dysfunction and multiple comorbidities. DDIs can be assessed based on information available at www.hep-druginteractions.org (http://www.hep-druginteractions.org/) [11]. This website was launched in 2010 by members of the Department of Pharmacology at the University of Liverpool to offer a resource for healthcare providers, researchers, and patients to be able to understand and manage drug-drug interactions. The fact sheets containing information on the pharmacokinetics, metabolism, and disposition of each drug are in PDF format. Data have been collected from company information, published literature, and are referenced at the end of each sheet. Since pharmacokinetic parameters are dependent on dose (and route of administration), data refer to the licensed dose unless otherwise stated.

According to the significance of interactions with DAA, DDIs were assigned to four risk categories as follows: classification not possible due to lack of information: category 0; no clinically significant interactions expected: category 1; significant interaction possible, may require dose adjustment/closer monitoring: category 2; and coadministration either not recommended or contraindicated: category 3. The regular comedication drugs were sorted into different groups according to the organ or system on which they act. When patient use more drugs with different risks for a DDI, the highest category was chosen to determine the risk for the patient with a respective treatment regimen. Also, the results are presented as a "Traffic Light" system (red, amber, and green) to indicate the recommendation. Last changes, made recently, include the new category, a yellow: potential interactions likely to be of weak intensity where additional action/monitoring or dosage adjustment is unlikely to be required [12].

DAAs may share metabolic pathways with drugs, such as antiretroviral drugs, cardiovascular drugs, lipid lowering drugs, immunosuppressive drugs, methadone, buprenorphine, herbal remedies, and commonly prescribed psychiatric medications, that are commonly used by populations with a high prevalence of hepatitis C. In the following text, we review drug interactions with some groups of drugs often used as comedications with DAAs in clinical practice.

4.1. Antiretroviral drugs

Coinfection with HIV and HCV is a serious problem resulting in many complications, including faster liver decompensation, cirrhosis, and hepatic carcinoma [4]. One-fourth of patients

infected with HIV concomitantly have HCV infection [13]. After introducing highly active antiretroviral drugs in therapy, liver complications became the leading cause of morbidity and mortality in HIV-HCV coinfected population.

Optimal treatment is necessary to avoid such complications. It is very important to address drug-drug interactions between these two regimens to avoid adverse effects and a decrease in efficacy, thereby increasing adherence to therapy. Some of DAAs (e.g. simeprevir, following fixed combination VEL/SOF, 3D, and EBR/GZR) are not recommended for use with many HIV antiretroviral (ARV) drugs as well as efavirenz, etravirine, and nevirapine. Sofosbuvir and fixed combination LDV/SOF can be safely administered with many antiretroviral drugs used to treat coinfections (HCV and HIV) (**Table 2**).

The combination ledipasvir/sofosbuvir can be used with all ARVs. However, these combinations should be used with frequent renal monitoring when a pharmacokinetic enhancer (ritonavir or cobicistat) is present in an ARV regimen due to an increase in tenofovir concentrations. Also, tenofovir concentration is increased in efavirenz-containing regimens and renal monitoring is necessary.

Class	Drug	BOC	TLP	SOF	DCV	SIM	LDV/SOF	VEL/SOF	3D	EBR/GZR
NRTIs	Abacavir									
	Emtricitabine									
	Lamivudine									
	Tenofovir									
NNRTIs	Efavirenz									
	Etravirine									
	Neviparine									
	Rilpivirine									
PIs	A; A/r; A/C									
	D; D/C									
	Lopinavir									
E/IIs	Doluteglavir									
	E/C/E/TDF									
	E/C/E/TAF									
	Maraviroc									
	Raltegravir									

NRTIs, nucleoside analog reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; E/I i, entry and integrase inhibitors; A, atazanavir; A/r, atazanavir/ritonavir; A/C, atazanavir/cobicistat; D, darunavir; D/C, darunavir/cobicistat; E/C/E/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; E/C/E/TA, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; LDV/SOF-ledipasvir + sofosbuvir; VEL/SOF-velpatasvir + sofosbuvir; 3D, ritonavir boosted paritaprevir + ombitasvir + dasabuvir; EBR/GZR, elbasvir + grazoprevir.

Green-no clinically significant interaction expected. Red-contraindication. Amber-potential interaction; dose adjustment, altered timing of administration, or require monitoring.

Adapted according to www.hep-druginteractions.org (University of Liverpool).

Table 2. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

4.2. Immunosuppressive agents (including steroids)

The most important drug interactions of DAAs are those with immunosuppressants, such as tacrolimus and cyclosporine [14]. These immunosuppressants are substrates of both CYP3A and P-gp, and inhibitory effects of boceprevir and telaprevir on CYP3A and P-gp increased plasma concentrations of the immunosuppressants. In particular, the interaction between tacrolimus and telaprevir had a magnitude that was unprecedented in clinical pharmacology: the AUC of tacrolimus is increased by 70.3-fold, and this combination would be lethal if doses were not adjusted [15]. From the start of combined treatment, therapeutic drug monitoring of immunosuppressants with dose adjustment can solve this problem (about 50% of observed differences in healthy volunteers) [16].

The combined therapy of telaprevir and boceprevir with systemically applied corticosteroids, such as methylprednisolone and prednisone, is not recommended due to risk of Cushing syndrome. These corticosteroids are CYP3A4 substrates and higher steroid levels can be expected. Similar situation is for locally applied corticosteroids by inhalation or intranasally such as fluticasone and budesonide. According to available data, beclomethasone can be used safely in patients on strong CYP3A inhibitors [16] and represents a corticosteroid of choice in patients with HCV therapy.

Also, sofosbuvir as DAAs in combination with daclatasvir or velpatasvir can be used when co-treatment is necessary with immunosuppressants or corticosteroids (**Table 3**).

Class	Drug	BOC	TLP	SOF	DCV	SIM	LDV/SOF	VEL/SOF	3D	EBR/GZR
Immunosupressives	Azathioprine									
	Cyclosporine									
	Everolimus									
	Mycophenolate									
	Sirolimus									
	Tacrolimus									
Corticosteroids.	Beclomethason									
	Dexamethasone									
	Momethasone									
	Prednisone									
	Methylprednisolone									
	Hydrocortsone top.									

LDV/SOF, ledipasvir + sofosbuvir; VEL/SOF, velpatasvir + sofosbuvir; 3D, ritonavir boosted paritaprevir + ombitasvir + dasabuvir; EBR/GZR, elbasvir + grazoprevir; top, topical.

Green-no clinically significant interaction expected. Red-contraindication. Amber-potential interaction; dose adjustment, altered timing of administration, or require monitoring.

Adapted according to www.hep-drugineractions.org (University of Liverpool).

Table 3. DDIs between DAAs and immunosuppressive agents (including corticosteroids).

4.3. Psychoactive agents

The prevalence of mental disorders remains high among untreated HCV-infected patients [17, 18]. In one retrospective study, the authors reported that 86% of HCV-infected patients had at least one psychiatric-, drug-, or alcohol use-related disorder recorded in their patient data. The most common conditions were depressive disorders (50%) and psychosis (50%), followed by anxiety disorders (41%), post-traumatic stress disorders (34%), and bipolar disorders (16%) [19]. The majority of DAAs are extensively metabolized by liver enzymes and have the ability to influence cytochrome P450 (CYP) enzymes, as well as majority of psychoactive medications. However, remarkably little information is available on DDIs between psychoactive medications and DAAs. Smolders et al. made overview of the interaction mechanisms between DAAs and psychoactive agents [20]. In addition, they described evidenced-based interactions between DAAs and psychoactive drugs and identified safe options for the simultaneous treatment of mental illnesses and chronic HCV infection [20]. Boceprevir, telaprevir, and the combination paritaprevir/ritonavir plus ombitasvir with dasabuvir were most likely to cause drug interactions by inhibition of cytochrome P450 (CYP) 3A4 [11]. Escitalopram and citalopram have been studied in combination with most direct-acting antivirals (DAAs) and either of these drugs can be safely combined with hepatitis

Drug	Drug	BOC	TLP	SOF	DCV	SIM	LDV/SOF	VEL/SOF	3D	EBR/GZR
Anti-depressants	Amitriptyline									
	Citalopram									
	Duloxetine									
	Escitalopram									
	Fluoxetine									
	Paroxetine									
	Sertraline									
	Trazodone									
	Trimipramine									
	Venlafaxine									
Antipsychotics	Amisulpiride									
	Ariprazole									
	Chlorpromazine									
	Clozapine									
	Flupentixol									
	Haloperidol									
	Olanzapine									
	Paliperidone									
	Quetiapine									
	Risperidone									
	Zuclopentixol									

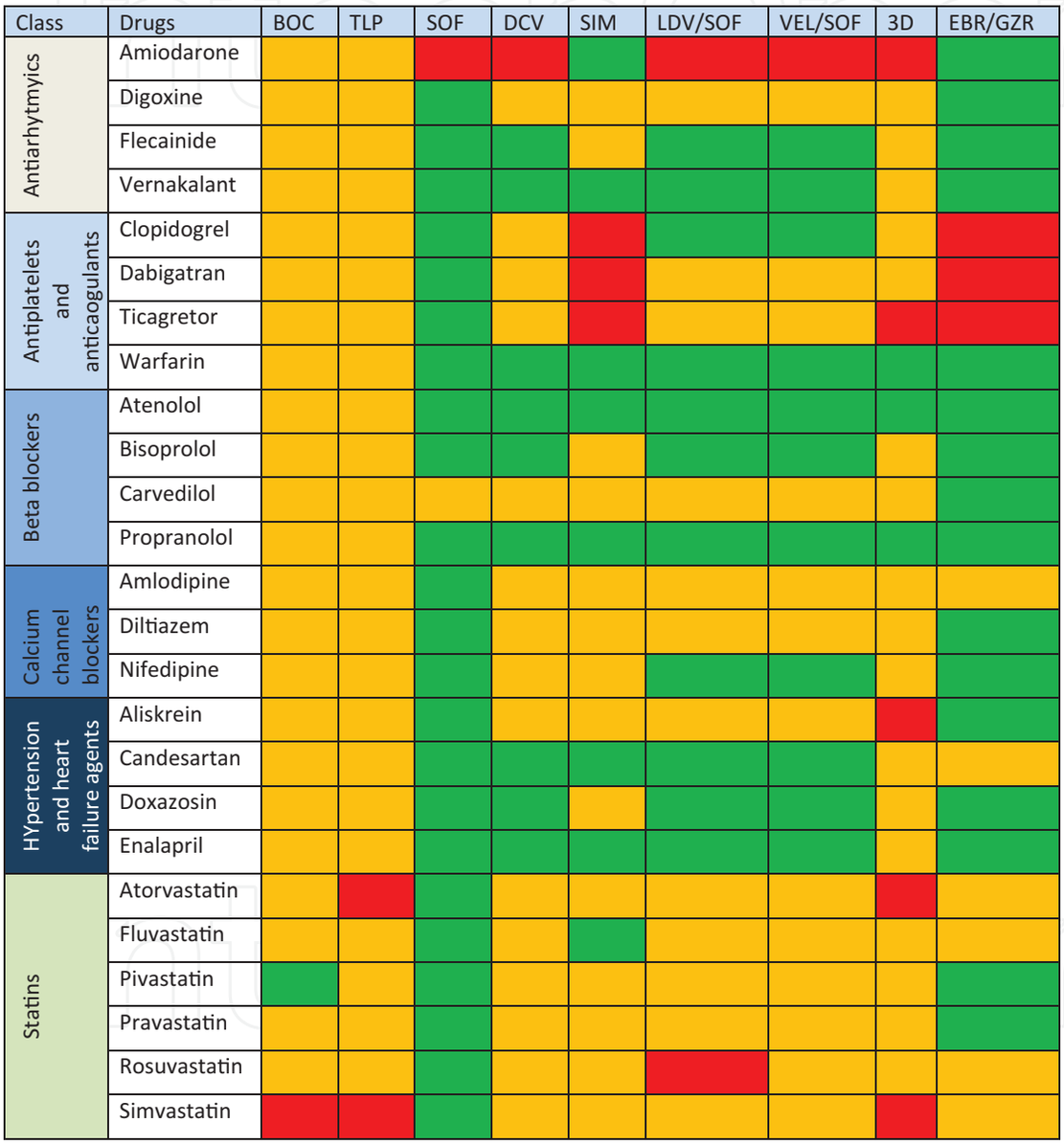
LDV/SOF, ledipasvir + sofosbuvir; VEL/SOF, velpatasvir + sofosbuvir; 3D, ritonavir boosted paritaprevir + ombitasvir + dasabuvir; EBR/GZR, elbasvir + grazoprevir.

Green-no clinically significant interaction expected. Red-contraindication. Amber-potential interaction; dose adjustment, altered timing of administration, or require monitoring.

Adapted according to www.hep-druginteractions.org (University of Liverpool).

Table 4. DDI between DAAs and psychoactive agents.

C virus (HCV) treatment besides boceprevir and telaprevir [11, 20]. No formal interaction studies between psychoactive agents and sofosbuvir or ledipasvir have been performed in humans. However, these DAAs are generally neither victims nor perpetrators of drug interactions and can, therefore, be safely used in combination with psychoactive drugs (**Table 4**) [11, 20].



LDV/SOF, ledipasvir + sofosbuvir; VEL/SOF, velpatasvir + sofosbuvir; 3D, ritonavir boosted paritaprevir + ombitasvir + dasabuvir; EBR/GZR, elbasvir + grazoprevir.

Green-no clinically significant interaction expected. Red-clinically significant interaction; contra-indication. Amber-clinically significant interaction; potential interaction-dose adjustment, altered timing of administration, or require monitoring.

Adopted according to www.hep-druginteractions.org (University of Liverpool).

Table 5. DDI between DAAs and cardiovascular drugs.

4.4. Cardiovascular drugs

Calcium channel blockers are CYP3A and partly P-gp substrates and, thus, increased exposure can be expected with CYP3A inhibitors. In that, sofosbuvir is drug of choice due to its metabolism by other metabolic pathways. Antiarrhythmics have a narrow therapeutic window, and some are CYP substrates (e.g. amiodarone). Amiodarone is contraindicated with many DAAs, except simeprevir and combination elbasvir/grazoprevir (**Table 5**). Digoxin has been tested with telaprevir as prototype of P-gp substrate. Levels of digoxin were increased by 85% with telaprevir, which is a moderate inhibitor [15]). Although, according to hep.interactions no clinically significant interactions between warfarin and DAAs, there is one case report in the available literature [21].

Many statins are both CYP3A substrates and inhibitors of telaprevir and boceprevir. DAAs are expected to increase statin levels and the associated risk of severe toxicity such as rhabdomyolysis [16]. Atorvastatin levels were elevated almost eight times with telaprevir, and this combination is contraindicated. Atorvastatin level were elevated 2.3 times with boceprevir, but this interaction can be manageable by staring with low dose of atorvastatin. In the case of pravastatin, levels were marginally increased when combined with boceprevir (1.5-fold), and it probably caused inhibition of OATP1B1. According to some clinicians, it is possible to temporarily stop the statins during relatively short treatment to avoid toxicity with DAAs.

4.5. Proton pump inhibitors (PPIs)

Depending on the DAA regimen, one of the most frequent drug classes involved in significant DDIs (category 2 or 3) is PPIs. Acid-reducing agents reduce the absorption of some DAAs (e.g. ledipasvir, velpatasvir) and, therefore, its serum concentrations. An observational study called Target has reported an association between the use of acid-reducing agents and decreased effectiveness of Harvoni (sofosbuvir-ledipasvir) [22]. In Target, participants who used PPIs had a cure rate of 93% vs. a cure rate of 98% in people who did not use PPIs. In that case, combination elbasvir/grazoprevir was a better choice (**Table 6**).

Class	Drug	BOC	TLP	DCL	SIM	SOF	LDV/SOF	VEL/SOF	3D	ELB/GRA
PPIs	Esomeprazole									
	Lansoprazole									
	Omeprazole									
	Pantoprazole									
	Rabeprazole									

LDV/SOF, ledipasvir + sofosbuvir; VEL/SOF, velpatasvir + sofosbuvir; 3D, ritonavir boosted paritaprevir + ombitasvir + dasabuvir; EBR/GZR, elbasvir + grazoprevir.

Green-no clinically significant interaction expected. Red-contraindication. Amber-potential interaction; dose adjustment, altered timing of administration, or require monitoring.

Adopted according to www.hep-druginteractions.org (University of Liverpool).

Table 6. DDI between DAAs and PPIs.

5. Real-life studies

The first real-life study with boceprevir and telaprevir was published in 2013 [23]. In this study, 101 patients were selected for treatment in one center. All changes to comedications before and during treatment were documented. Drugs were checked for DDIs with telaprevir and boceprevir using DDI website resources and categorized into groups according to traffic lights (red, amber, and green). Similar to the general population, HCV patients often suffered from various common comorbidities like hypertension, dyslipoproteinemia, or atrial arrhythmia. Furthermore, some comorbidities like diabetes and thyroid disorders may even be overrepresented in the HCV-infected population. There was no clinically significant risk in 62% drugs, whereas for 29% drugs, some DDI were suspected. However, dose modifications or careful monitoring were sufficient for management. Only 4% of drugs were contraindicated for co-administration with DAAs. However, 10% of patients took one of these contraindicated drugs. Fourthy nine of patients were suspected to be at risk for experiencing significant DDIs. Drug classes most often suspected to be involved in significant DDI were thyroid hormones, dihydropyridine derivatives, and herbal/alternative drugs. In 16% of the patients, at least one drug of the regular outpatient medication was stopped before DAA treatment. Overall, suspected DDIs were managed by dose adjustments and discontinuation of comedication before or during DAAs therapy in 75 and 21% of the patients.

After this study, the other real-life studies were published. They include monoinfected HCV group, coinfected HIV/HCV group, and elderly patients with different severity of liver disease [24–27]. In all studies, the potential for DDIs between DAAs and comedications was assessed using www.hep-druginteractions.org. In the real-word large cohort study, Ze Siederdissen et al. assessed significance of DDIs between DAAs therapies and regular medications. During the period between 2011 and 2014, 261 patients with HCV were selected for DAAs therapy and asked for their regular outpatient therapy. Twenty percent of patients did not use any comedications. The median number was two drugs (range 0–15). The highest risk to cause significant DDIs had ombitasvir/paritaprevir/ritonavir ± dasabuvir (66.3%), in contrast with sofosbuvir/ribavirin that possessed lowest risk (9.6%). Significant DDIs for sofosbuvir/ledipasvir would be expected in 40.2%, for sofosbuvir/daclatasvir in 36.8%, and for sofosbuvir/simeprevir in 31.4%. The most frequently used comedication drugs that possess risk of DDIs were proton pump inhibitors, thyroid hormones, and dihydropyridine derivatives.

Gussio et al. assessed the clinical significance of DDI with DAA in a real-world polycentric retrospective study involving five clinical unit of infectious diseases in south of Italy and Sardinia treating HCV monoinfected and coinfected subjects selected for DAA therapy [25]. Two hundred and fifteen (215) subjects were enrolled in the study. Of the total, 139 were HCV monoinfected and 76 HIV coinfected. One hundred and seventy patients (170 or 75%) were males; median age was 55 years with stage of fibrosis F4 in 70% of patients. At least one comorbidity was found in 146 patients (68 and 67%, respectively, within mono and HIV coinfected). HCV monoinfected and HIV coinfected subjects had medians of 2 and 1 comorbidities, respectively. Regarding DAA drug-drug interactions, sofosbuvir/daclatasvir had the lowest risk to cause a potentially significant DDI (20%). In contrast, for ombitasvir/paritaprevir/ritonavir ± dasabuvir, there was potentially significant DDIs (49.8%). Significant DDIs

for sofosbuvir/simeprevir were expected in 30.8%, for sofosbuvir/ribavirin in 28.2%, and for sofosbuvir/ledipasvir in 39.8%. Proton pump inhibitors, diuretics, and some antihypertensive drugs were frequently used and presented a risk of interacting with the antiviral regimen. Antiretroviral regimens also showed a high risk of potential interactions, although 16% of patients had preventively modified this treatment.

Kondili et al. assessed the potential DDIs of DAAs in HCV-infected outpatients. They evaluated 449 patients in 25 clinical centers in one Italian prospective multicenter study [26]. Patients started a DAA regimen and received comedications between March 2015 and March 2016. From total number of patients, 86 had mild liver disease and 363 had moderate-to-severe disease. The utilization of more than three drugs was more frequent in the patients with moderate-to-severe disease, whereas the use of single drug as a comedication was more frequent in patients with mild liver disease. About 30% (26/86) of patients with mild liver disease used at least one drug with a potential DDI, whereas 44% (161/363) of patients with moderate-to-severe liver disease were at risk for one or more DDI. Twenty percent of drugs (27/142) used as comedications in 86 patients with mild disease may require dose adjustment or closer monitoring, whereas none was contraindicated. Twenty five percent (82/322) of comedicated drugs in 363 patients with moderate-to-severe liver disease were classified as potential DDOs that required monitoring and dose adjustments and 3% (10/322) were contraindicated in severe liver disease. Patients with moderate-to-severe liver disease require much more attention due to potential DDI during DAA therapy according to the data from this study.

Direct antiviral therapies for chronic hepatitis C virus (HCV) infection have expanded treatment options for neglected patient populations, including elderly patients who are ineligible/intolerant to receive interferon (IFN)-based therapy. Vermehren et al. followed 541 patients treated with different combinations of direct antiviral agents (DAAs: ledipasvir/sofosbuvir ±ribavirin; daclatasvir/sofosbuvir ±ribavirin; paritaprevir/ombitasvir ±dasabuvir ±ribavirin or simeprevir/sofosbuvir ±ribavirin or sofosbuvir/ribavirin in genotype) [27].

SVR rates were 91 and 98% in patients aged <65 years and ≥65 years, respectively. Elderly patients took significantly more concomitant drugs (79% vs. 51%). Patients over the age of 65 years with cirrhosis took the highest number of concomitant medications (three per patient-median; range, 0–10).

The number of patients who experienced treatment-associated adverse events was similar between the two age groups (63% vs. 65%). However, proportion of predicted clinically significant DDIs was significantly higher in elderly patients (54% vs. 28%). Elderly patients are at increased risk for significant DDIs when treated with DAAs for chronic HCV infection.

6. Conclusions

Based on these findings, a careful assessment of the regular outpatient medication (all drugs, including herbal products/alternative medicines and even illegal drugs e.g. HIV patients/intravenous users) and subsequent evaluation of potential DDIs with DAAs are absolutely

crucial to ensure drug safety in all treated patients. Web-based DDI tools like www.hep-druginteractions.org represent the best way for an assessment of potential DDIs. However, although this web resource includes a huge number of drugs and regular update, some of the drugs are not probably covered.

Also, it is impossible to foresee each combination of drug used in the treatment, and data from real life are also useful source of information. Some DDIs may occur unexpectedly despite a careful evaluation before starting treatment, as demonstrated by the EMA and FDA warning against the concomitant use of amiodarone- and sofosbuvir-containing DAA therapy due to the occurrence of potentially life-threatening bradycardia.

In summary, thousands of patients are being treated with DAAs and a significant number of patients are at risk for DDIs. Although the use of strictly contraindicated comedications seems to be rare, a careful assessment of regular medications and a comprehensive evaluation of potential DDIs with each DAA used for therapy are essential to prevent adverse effects or unnecessary risks of treatment failure.

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