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Toxicity and risks from drug-to-drug interactions of new antivirals for chronic hepatitis C

C. BINDA, A. TORTORA, M. GARCOVICH, B.E. ANNICCHIARICO, M. SICILIANO

Gastroenterologic Area, Policlinico Gemelli, Catholic University of the Sacred Heart, Rome, Italy

Abstract. – The new direct acting antivirals (DAAs), defined as those drugs that are effective in combinations without interferon, have totally changed HCV treatment and probably in few years will also totally change global landscape of advanced liver diseases. The advantage of DAAs is a low-risk/high-benefit ratio. Although overall adverse events during DAAs treatment are limited in frequency and severity, some toxicity issues emerged during the first years of real-life experience with these drugs. Another peculiar characteristic of present DAAs is a high probability of interaction with other "common-use" drugs, such as anti-hypertensive, anti-platelet, antiarrhythmic and cholesterol lowering agents. Above all, special attention should be paid in older patients and in those belonging to special populations, who more frequently require the concomitant use of polytherapy.

Key Words
DAAs, Drug-to-drug interaction, Drug toxicity, HCV.

Introduction

In the last years, we have assisted to a revolution in HCV-infection' s therapy, passing from 25 years of the interferon-based regimen to new direct acting antivirals (DAAs). In contrast to the non-selective action of the interferon based-regimen, these new molecules are targeted to specific non-structural proteins of the virus causing disruption of viral replication and infection[1]. The main classes of DAAs are represented by NS3/4A protease inhibitors, NS5A polyprotein inhibitors, NS5B polymerase inhibitors.

While interferon-based regimen were burdened by severe adverse events and inconsistent results, the new DAAs demonstrated a high efficacy in obtaining sustained virological response and high tolerability profiles, due to oral administration and low rates of side effects. These characteristics promote the large diffusion of DAA within the HCV-infected population and broaden the indications of treatment to those categories of patients that were previously excluded for severity of hepatic disease, co-morbidities, and co-medications. Thus, in real life-experience are emerging toxicities and drug-to-drug interactions that did not come to light during phase-three studies or that were underrated. Hence, in clinical practice, we have to face these new scenarios especially in those patients considered as a special population, like HCV/HIV co-infected patients, patients with decompensated cirrhosis, waiting-list patients, and transplant recipients.

Herein, an excursus, based on recent literature, of toxicity and drug-to-drug interaction of the main regimens employed for HCV-infection.

Sofosbuvir

Sofosbuvir (SOF), Sovaldi® in EU, is a NS5B polymerase inhibitor used as the backbone of different DAAs regimens. It is very well tolerated causing few adverse effects, such as fatigue, nausea, insomnia, headache, anemia, pruritus and dizziness[2-4], that occur more frequently when it is used in association with ribavirin (RBV).

Because of its primary elimination by the kidney as an inactive metabolite, the GS-331007 [5], its use is not recommended in patients with creatinine clearance less than 30 ml/min and patients on hemodialysis[6-9].

Within the main interactions that came to light in real life experience, the one with amiodarone demonstrated to be associated with serious and life-threatening slowing of the heart rate[10]. Fon-

Corresponding Author: Massimo Siciliano, MD; e-mail: massimo.siciliano@policlinicogemelli.it

taine et al reported three cases of symptomatic bradycardia occurred within the first 10 days of treatment with SOF due to sinus-node dysfunction or intermittent third-degree atrioventricular block[11]. In one of the three patients, the sinus-node dysfunction resolved after discontinuation of treatment with SOF/Simeprevir and amiodarone, but recurred after 6 days by the reintroduction of SOF (without Simeprevir). All the three patients were treated with the pacemaker implant. Therefore, the concomitant administration of SOF with another DAA and amiodarone or the administration of SOF and another DAA in subjects who discontinued amiodarone within the past few months should be avoided. If alternative anti-arrhythmic treatments are not tolerated or are contraindicated, the use amiodarone during SOF-based regimen is allowed, but a continuous monitoring of 48 hours in an appropriate clinical setting is recommended[12].

Case-series of newly diagnosed or worsening of pulmonary arterial hypertension (PAH) in patients treated with SOF have been reported[13,14]. However, it is still difficult to identify the link between SOF and PAH, because the majority of those patients had concomitant PAH risks factors, like portal hypertension and/or HIV infection. Interestingly, in the French series[14], PAH was reversible without PAH-targeted therapy in the patient who was asymptomatic and without portal hypertension before exposure, whereas it was not totally reversible in spite of PAH-targeted therapy in those who were asymptomatic before exposure but had portal hypertension.

Many studies demonstrated that SOF-based regimens are effective even in patients with decompensated cirrhosis and in transplant recipients, with high rates of SVR, low rates of side effects and improvement of Child-Pugh and MELD scores in some decompensated subjects who achieved SVR 12[15-17].

Patients with advanced liver disease have an increased risk of lactic acidosis, which can in part be explained by potentially decreased hepatic lactate clearance[18,19]. Welker et al reported the occurrence of lactic acidosis associated with acute-on-chronic decompensation during SOF/RBV antiviral regimen, including renal failure and/or infectious complications[20]. It had also been shown that several nucleoside inhibitors are associated with mitochondrial toxicity, including lactic acidosis, especially when administered in association with antiretroviral therapy in HCV/HIV co-infected patients[19,21-23]. Furthermore, SOF had been associated with elevated lipase levels that could be interpreted as an indicator of mitochondrial toxicity[8,24].

SOF is a substrate of the P-glycoprotein (P-gp) drug transporter, so that its levels may be decreased by concomitant use of potent intestinal P-gp inducers, like rifampicin, rifabutin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital, or ritonavir.

In general, SOF causes few and non-severe side effects and has low rates of drug-to-drug interactions [24], so that it can be probably considered one of the safest and manageable DAA for HCV. However, attention should be paid to avoid interaction with amiodarone, in patients with advanced liver disease and those with pulmonary hypertension.

Simeprevir

Simeprevir (SMV) is the first available second-generation NS3/4A protease inhibitor that exhibits its effect through reversible binding of the NS3 protease active site and that is usually used in combination with sofosbuvir. The most common side effects experienced by patients are fatigue, headache, pruritus, influenza-like illness, nausea, myalgia, and dyspnoea[25-28]. Simeprevir is photodynamically active, absorbing UV-B (290-320 nm) and UV-A (320-400 nm) light, suggesting a phototoxicity rather than photoallergy[29,30]. This determines a photosensitivity reaction that increases in a dose-dependent manner and that may lead to temporary or permanent treatment cessation, even in patients using sun-protective measures[29-31].

Another clinically significant adverse event is hyperbilirubinemia, that is usually mild and transient and represented mainly by unconjugated bilirubin[25,26,32]. Simeprevir, indeed, is a potent inhibitor of OATP1B1, transporter of indirect bilirubin into liver cells, and a mild inhibitor MRP2, transporter of direct bilirubin out of hepatocytes, causing predominantly an increase in plasmatic unconjugated bilirubin, rather than conjugated[33-35].

Simeprevir has mainly a hepatic metabolism so that its use is not recommended in patients with moderate or severe liver impairment (Child-Pugh class B and C) because of an augmented AUC[31,36,37]. Stein et al reported two cases of cholestatic liver injury during compassionate treatment with SMV/SOF in patients affected by

decompensated cirrhosis, with early discontinuation of treatment[38].

Simeprevir is metabolized by CYP3A4 so that its concomitant use with CYP3A4 inhibitors, like ritonavir, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, rifabutin, may cause prolonged therapeutic effects and higher risks of adverse events[33,36,39]; indeed, the simultaneous administration of CYP3A4 inducers can compromise its therapeutic effects. Lastly, Simeprevir inhibits gut CYP3A4, intestinal efflux transporter P-gp and OATP1B1/3, causing, for example, increased levels of rosuvastatin and atorvastatin (substrates of OATP1B1/3)[33,36,39].

Ledipasvir/Sofosbuvir

Ledipasvir (LDV) is an inhibitor of HCV-encoded NS5A polymerase, administered in fixed combination with SOF, Harvoni® in EU, with or without weight based RBV. As SOF, it is well tolerated with very few side effects usually from mild to moderate in severity[40]; they are more frequent in RBV-containing regimens and represented by fatigue, headache, nausea, insomnia, and diarrhea[41]. An increased incidence of hyperbilirubinemia was reported in patients receiving LDV/SOF with RBV, while no such effect was observed in the RBV-free counterparts[41]. Severe renal impairment does not substantially affect the pharmacokinetics of LDV, but the association with SOF makes this regimen contraindicated in such patients for the increased level of GS-331007 (SOF metabolite), as above-mentioned. However, a case of acute allergic interstitial nephritis (AIN) LED/SOF-associated, proven by kidney biopsy, was pointed out[42].

It had also been hypothesized that the interaction between LDV and TDF could determine increased levels of TDF and subsequently a nephrotoxicity in a patient with HCV/HIV co-infection[43]. Thus, guidelines for the treatment of HCV recommend avoidance of LDV/SOF and TDF combination when creatinine clearance is < 60 ml/minute[44].

Furthermore, a single case of myopericarditis secondary to LDV/SOF therapy was reported, but the mechanism of this cardiotoxicity is still unclear[45].

While SOLAR 1 and SOLAR 2 studies showed how LDV/SOF regimen can be safely used in patients with decompensated cirrhosis, there are many reports of liver toxicity in decompensated patients, especially in HCV/HIV co-infected ones[46-50], probably due to the interaction between LDV/SOF and antiretrovirals[51]. One of the mechanisms that can explain these interactions is the increased absorption of P-glycoprotein (P-gp) substrates, because of LDV inhibition of P-gp[51]. Like SOF, LDV is a substrate of the P-gp drug transporter; thus its plasma level can be decreased by P-gp inducers like rifampicin, rifabutin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital or ritonavir. The risk of drug-to-drug interaction was also observed with proton pump inhibitors (PPIs), dihydropyridine derivatives ad alpha and beta blocking agents[40]. Increased gastric pH levels may decrease absorption of LDV, reducing the exposure of the drug by more than 50% if the PPI is taken 2 hours before LDV[52]. This DDI can be prevented by a simultaneous intake of both drugs. A recent real-world cohort study suggests that twice-daily PPIs use is associated with a lower odds ratio for SVR12[53].

Daclatasvir

Daclatasvir (DCV), Daklinza® in EU, is a NS5A inhibitor used in combination with SOF. It is usually well tolerated, with very few side effects, mild to moderate in severity, such as headache, fatigue, and nausea[54,55].

It is primarily metabolized by CYP3A and it is a mild inhibitor of P-gp, OATP1B1, and BCRP. No dose adjustment is required for renal neither hepatic impairment, but it may be needed when DCV is administered with other medications. A dose reduction to 30 mg once daily, indeed, is recommended when DCV is used with strong CYP3A inhibitors like ritonavir-boosted atazanavir, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, rifabutin, calcium channel blockers (diltiazem, nifedipine, amlodipine, and verapamil)[56-60]; instead, a dose increase to 90 mg once daily is recommended when DCV is used with moderate CYP3A inducers such as efavirenz, dexamethasone, carbamazepine, phenobarbital, phenytoin, and St. John's worth (hypericumperforatum)[56-60].

Because of the DCV-based inhibition of P-gp, OATP1B1, and BCRP, during co-administration with DCV caution should be paid to the risk of increased exposure to digoxin, dabigatran etexilate, and HMG-CoA reductase inhibitors, like rosuvastatin, pravastatin, simvastatin, atorvastatin[57].

Furthermore, DCV showed a PH-dependent

solubility, indicating a potential slower absorption in the presence of acid-reducing agents. However, no meaningful decreased exposure was observed during the co-administration with omeprazole[61].

A phase 3 evaluation in post-transplant recipients with HCV recurrence demonstrated how DCV is highly effective and well tolerated, requiring immune-suppressants dose-adjustment only in one patients[16].

Ombitasvir/Ritonavir/Paritaprevir with/without Dasabuvir

Ombitasvir(OBV) is a NS5A inhibitor administered in fix-dose combination with paritaprevir (PTV), a NS3/4A protease inhibitor metabolized by CYP3A, and ritonavir (r), Viekirax® in EU. Ritonavir does not have a direct anti-HCV activity but is included to increase levels of PTV though the inhibition of CYP3A-metabolism. Dasabuvir (DSV), Exviera® in EU, is a non-nucleoside polymerase inhibitor metabolized by CYP2C8. OBV/PTV/r plus DSV with or without weight based RBV is approved for HCV genotype 1 infection, while OBV/PTV/r plus RBV without DSV is effective in genotype 4 infected patients.

The most common side effects reported in the literature are nausea, pruritus, insomnia, diarrhea, asthenia, fatigue, and headache. Side effects occur especially when ribavirin is associated[62-64]. Trials comparing the regimen with and without ribavirin highlighted that pruritus, nausea, insomnia ad rash are more frequent among patients that received RBV[65,66].

As most frequent clinically significant abnormality, the main studies reported grade 3-elevated (more than 3-10 times the upper limit of the normal range) total bilirubin levels, predominantly indirect bilirubin, which usually improves or resolves without discontinuation of therapy[62,63,65,67,68]. Less than 1% of patients ranged ALT levels more than 5-20 or more than 20 times the upper limit of the normal range, showing peak values generally within the first two weeks of treatment and a declining to normal range with ongoing treatment.

Ferenci et al[65] showed that comparing to the counterparts "RBV-free", a higher proportion of patients receiving the RBV-containing regimen had elevated serum bilirubin levels, regardless of genotypic subtype; the mean peaks were reached 1 week after the start of treatment and normalized thereafter. The elevation in bilirubin levels was not associated with an elevation in aminotransferase levels, and these abnormalities appeared to affect neither the likelihood of treatment success rate nor rate of treatment discontinuation.

As mentioned above, all these drugs have a primarily hepatic metabolism. This is a possible cause of the hepatic decompensation associated with this treatment in patients with underlying cirrhosis[69]. Most cases occurred within one to four weeks after drug initiation, and some cases resulted in the need of liver transplantation or in death. Hence, the use of this regimen is contraindicated in moderate to severe liver impairment (Child-Pugh classes B and C), while it is allowed in Child-Pugh A patients without dose adjustment, although a close monitoring for signs of decompensation is recommended[69-71].

On the other hand, the use of OBV/PTV/r and DSV is considered effective and safe in patients with renal failure, with a eGFR<30 ml/min and in dialysis. The RUBY-1 study[72] considered non-cirrhotic patients with HCV genotype 1 infection with severe renal impairment (eGFR<30 ml/min), including those on dialysis, treated with OBV/PTV/r and DSV with or without RBV for 24 weeks; the study found out that this regimen is effective in such patients, with very low rates of adverse events that were from mild to moderate in severity, and without the need of treatment discontinuation. However, patients who received ribavirin had more frequent side effects, likely directly related to the ribavirin, including anemia, fatigue, nausea and diarrhea, and 8 of 13 patients interrupted ribavirin during the treatment course.

PTV and ribavirin are primarily metabolized by CYP3A, while DSV is metabolized by CYP2C8; in addition, OBV, PTV and ribavirin are all substrates of P-gp. Hence, the concomitant use of CYP3A, P-gp and CYP2C8 inhibitors may lead to an increased plasma concentration of PTV and r, OBV, PTV and r, and DSV, respectively[68]. Anticonvulsant, rifampicin, St. John's wort (Hypericum perforatum) and salmeterol shouldn't be co-administered with such regimens[69]. It was also observed a possible drug-to-drug interaction with ethinylestradiol-containing medications: 26% of women taking concomitant use of these drugs experienced serum alanine aminotransferase levels greater than five times the upper limit of normal range after starting treatment[71].

In a large real-world cohort study, the most frequent interactions were documented with proton pump inhibitors, thyroid hormones, and dihydropyridine derivatives; interestingly, the

addition of DSV did not change the number of patients affected by significant drug-to-drug interactions[24].

New second generation DAAS

Elbasvir/Grazoprevir

Elbasvir (EBR) is an NS5A inhibitor, that is associated in a fix-dose combination with the NS3/4A protease inhibitor grazoprevir (GZR). The EBR/GZR combination, Zepatier® in EU, demonstrated high efficacy against genotype 1, 4 and 6 and a high barrier of resistance, but very few adverse events, usually represented by fatigue, headache, and nausea[73-75]. The great advantage of this regimen consists in his approval even in patients with any degree of renal impairment, including those on dialysis[76].

Moreover, its efficacy was proven even in patients with advance liver disease, although a monitoring of aminotransferases is recommended particularly in Child-Pugh class B and C patients[73-77]. In fact, in approximately 1% of patients can occur a late elevation of aminotransferases, that can reach five times the upper limits of normal range. The regimen should be discontinued if aminotransferases elevation is accompanied by other signs or symptoms of hepatic injury.

Both EBR and GZR are metabolized by CYP3A and GZR is also a substrates of OATP1B1/3, so that the use of this regimen is contraindicated during the co-administration of inducers or inhibitors of CYP3A and inhibitors of OATP1B1/3, such as rifampicin, phenytoin, carbamazepine, St. John's wort (Hypericum perforatum), cyclosporine, ritonavir, and efavirenz.

Velpatasvir/Sofosbuvir

Velpatasvir (VEL) is a pangenotypic NS5A inhibitor, given in fix-dose association with SOF once daily, Hepclusa® in EU. Its efficacy had been demonstrated against all genotypes, even in patients with liver impairment, without dose adjustment, causing low rates of side effects, such as headache, fatigue, nausea, nasopharyngitis and insomnia[78-81]. Its use in patients with severe renal impairment is still under debate, due to the increased levels of SOF and its metabolite in this setting.

VEL is a substrate of P-gp drug transporter, so that its use is contraindicated with rifampin, phenytoin, phenobarbital, carbamazepine, St. John's wort (Hypericum perforatum), ritonavir. Lastly, the use of proton pump inhibitor can decrease absorption of VEL/SOF because of the increased gastric pH levels.

Conclusions

The new direct acting antivirals are not risk-free therapy, as it is emerging from recent literature and the first real-life studies. However, comparing to interferon-based regimen, the adverse events, drug-to-drug interaction, and toxicity are lower in frequency and intensity, so that, when they occur, they usually do not require the discontinuation of treatment and do not condition the rate of response. In fact, DAAs are well tolerated by the majority of patients, who often refer nonspecific symptoms without a great impact on the quality of life and daily activities. However, when ribavirin is associated, the incidence of side effects and toxicity can reach higher percentage, but usually, this does not result in higher rates of drop-out, also because of the brief duration of such therapies (from 8 to 24 weeks).

Moreover, the high tolerability and safety of DAAs allow the treatment of special populations that were excluded from any kind of treatment in the era of interferons, such as HIV/HCV co-infected patients, patients with liver and renal impairment. These categories, however, have higher risks of drug-to-drug interaction and toxicity due to the higher number of co-medication and the burden on liver metabolism of the majority antivirals. Therefore, in these patients, a closer monitoring is recommended, combined with a strict indication and choice between the different regimens.

Nevertheless, are now available many sites that may help to unravel the knot of drug-to-drug interactions of DAAs. Among these, the more accredited are http://www.hep-druginteractions.org/checker and http://www.dpic.org/links/medscape-drug-interaction-checker. In our opinion, they represent a fundamental aid in the daily practice for the check of drug-to-drug interactions for any kind of co-medications, both chronic and extemporary therapies that may be needed throughout the duration of therapy with DAAs.

For these reasons, in the next few years we have to look forward an eradication plan, considering the enlargement of population eligible to these treatments[82] and the likely price reductions of drugs already estimated[83].

Table I. Main pharmacological characteristics of direct acting antivirals for HCV.

Molecule	Target	Associations	Substrate of	Effect on cytocrome and proteins
Sofosbuvir	NS5B RNA-dependent RNA polymerase	Ledipasvir Daclatasvir Simeprevir Velpatasvir	P-gp	None
Simeprevir	NS3/4A protease	Sofosbuvir	CYP3A4	↓ CYP3A4 ↓P-gp ↓OATP1B1/3
Ledipasvir	NS5A	Sofosbuvir	P-gp	↓P-gp
Daclatasvir	NS5A	Sofosbuvir	CYP3A4	↓ P-gp ↓OATP1B1 ↓BCRP
Paritaprevir	NS3/4A protease	Ombitasvir+Ritonavir with or without Dasabuvir	CYP3A4 CYP3A5	↓ CYP2C8
Ombitasvir	NS5A	Paritaprevir+Ritonavir with or without Dasabuvir	CYP3A4 P-gp	↓ CYP2C8
Dasabuvir	NS5B RNA-dependent RNA polymerase	Ombitasvir+Paritaprevir +Ritonavir	CYP2C8 CYP3A4* CYP2D6* *in minor part	None
Elbasvir	NS5A	Grazoprevir	CYP3A4	None
Grazoprevir	NS3/4A protease	Elbasvir	CYP3A4 OTA1B1/3	↓ CYP3A4 ↓ CYP2C8
Velpatasvir	NS5A	Sofosbuvir	P-gp	↓ P-gp

Table II. Side effects reported in real-life.

MOLECULE	Major side effects	Note
Sofosbuvir	Fatigue, nausea, insomnia, headache and anemia, pruritus and dizziness	More frequent in ribavirin-containing regimen
	Worsening of pulmonary arterial hypertension	
	Symptomatic bradycardia	Amiodarone
	Risk of lactic acidosis	Advanced liver disease or ribavirin association
	Elevated lipase levels	
Simeprevir	Fatigue, headache, pruritus, influenza-like illness, nausea, myalgia and dyspnea	Most common
	Photosensitivity reaction	
	Hyperbilirubinemia	
Ledipasvir/Sofosbuvir	Fatigue, headache, nausea, insomnia, and diarrhea, hyperbilirubinemia	More frequent in ribavirin-containing regimen
	Severe renal impairment	
	Myo-pericarditis	Case-report
	Liver toxicity	Patients with decompensated cirrhosis, especially in HCV/HIV coinfected patients
Daclatasvir	Not reported	
Ombitasvir/Ritonavir/ Paritaprevir with/ without Dasabuvir	Nausea, pruritus, insomnia, diarrhea, asthenia, fatigue and headache	More frequent in ribavirin-containing regimen
	Grade 3-elevated total bilirubin levels, predominantly indirect bilirubin	
	Increase ALT levels	
	Possible hepatic decompensation	Contraindicated in moderate to severe liver impairment (Child Pugh classes B and C), while it is allowed in Child Pugh A patients without dose adjustment, although a close monitoring for sign of decompensation is recommended
Elbasvir/Grazoprevir	Fatigue, headache and nausea	Data only from trials
	Late elevation of aminotransferase	
Velpatasvir/Sofosbuvir	Headache, fatigue, nausea, nasopharingitis and insomnia	

Conflict of Interests
The Authors declare that they have no conflict of interests.

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