ORIGINAL ARTICLE

DRUG-DRUG INTERACTION (DDI) TOOLS – USEFUL *VERSUS* MANDATORY IN THE MANAGEMENT OF DIFFICULT TO TREAT PATIENTS WITH CHRONIC HCV INFECTION

ANCA STREINU-CERCEL[1,2], OANA SANDULESCU[1,2]*, DANIELA MANOLACHE[2], MONICA ANDREEA STOICA[2], LILIANA LUCIA PREOȚESCU[1,2], ADRIAN STREINU-CERCEL[1,2]

[1] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2] *"Prof. Dr. Matei Balș" National Institute for Infectious Diseases, Bucharest, Romania*

**corresponding author: oanasandulescu1@gmail.com*

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Abstract

The treatment of chronic HCV infection has been redesigned with the advent of direct-acting antivirals which substantially increase the rate of sustained virological response but also entail new challenges – potential drug-drug interactions (DDIs) that may compromise antiviral efficacy or put the patient at risk for toxicity or under-treatment of comorbidities. We collected data on DDIs in the real-life treatment of chronically HCV-infected patients with the 3D regimen containing ombitasvir/paritaprevir/ritonavir plus dasabuvir, in a compassionate study approved by the Romanian National Agency for Medicines and Medical Devices. DDIs were checked with the HEP-Drug Interaction Charts, University of Liverpool (UK). Out of 44 patients, 14 (31.8%) had no comorbidities and 19 (43.2%) had no concomitant medications. After the DDI check, 14 (56%) of the 25 patients on co-medication did not require any intervention apart from close monitoring, 6 (24%) required dose adjustment, in 3 cases (12%) co-medication was changed and in 2 cases (8%) it was stopped during treatment of HCV infection. We identified more advanced baseline liver fibrosis in patients for whom co-medication needed changing ($p = 0.001$, $d = 6.9$), and in those who had comorbidities ($p = 0.036$) or required co-medication ($p = 0.001$). In conclusion, the 3D regimen displayed a good DDI profile in real-life settings, but close monitoring and accountability of co-medications should be performed by all treating physicians.

Rezumat

Tratamentul infecției cronice cu VHC a fost revoluționat de noile antivirale cu acțiune directă, care cresc semnificativ rata de răspuns virusologic susținut, însă pot aduce noi provocări – potențiale interacțiuni medicamentoase (DDI) care pot compromite eficacitatea antivirală sau pot asocia un risc de toxicitate sau de subdozare a medicamentelor utilizate în tratamentul comorbidităților. Am analizat interacțiunile medicamentoase identificate la pacienții cu infecție cronică VHC tratați în clinică cu moleculele 3D pe bază de ombitasvir/paritaprevir/ritonavir plus dasabuvir în cadrul unui studiu pentru tratament de ultimă instanță aprobat de către Agenția Națională a Medicamentului și Dispozitivelor Medicale. Interacțiunile au fost verificate cu ajutorul HEP-Drug Interaction Charts, Universitatea Liverpool, Marea Britanie. În rândul celor 44 de pacienți incluși în studiu, 14 (31,8%) nu aveau comorbidități și 19 (43,2%) nu aveau medicație concomitentă. După verificarea interacțiunilor, 14 (56%) dintre cei 25 de pacienți cu medicație concomitentă nu au necesitat o intervenție specifică, fiind suficientă monitorizarea tratamentului, 6 (24%) au necesitat o ajustare a dozei, 3 (12%) schimbarea și 2 (8%) oprirea medicației concomitente pe durata tratamentului anti-VHC. Am identificat o fibroză mai avansată la pacienții la care a fost necesară schimbarea medicației concomitente ($p = 0,001$, $d = 6,9$), dar și la cei care prezentau comorbidități ($p = 0,036$) și medicație concomitentă ($p = 0,001$). Tratamentul 3D a prezentat un profil bun în ceea ce privește interacțiunile medicamentoase în clinică, însă este necesară monitorizarea și verificarea atentă a medicației concomitente de către medicul curant.

Keywords: DDI, hepatitis C, interactions, paritaprevir, DAA

Introduction

The treatment of chronic HCV infection has recently been completely redesigned, with the advent of new therapeutic options, most of them interferon-free [10, 12], and with the possibility for individualized pharmacogenetic assessments [2, 3, 15]. Patients now have access to direct-acting antivirals (DAAs) which substantially increase the rate of sustained virological response, ensure better adherence compared to interferon-based regimens [13], but also entail new challenges, namely potential drug-drug interactions (DDIs) which can decrease either the effectiveness of the HCV drug (with subsequent risk of viral resistance), or that of the concomitant medication (and leave the patient's comorbidities not treated or incompletely treated). Moreover, in extreme cases, DDIs can put the patient at risk of toxicity through overdosing by

mechanism of reduced metabolization or clearance of the drug.

Clinical trials represent a mandatory step prior to approval of any new drug, and transferring knowledge from these studies to real-life settings can sometimes be challenging and the results may not always overlap. The background supports that subjects and investigators (patients and doctors in real-life settings) receive when they are involved in a clinical trial requires a lot of resources, material and human alike, in order to achieve the needed level of accuracy for the data to be processed and analysed. Transferring all these resources into real-life clinical practice may at times prove difficult. Moreover, the "ideal" subject included in the clinical trial (i.e., the patient with a controlled list of comorbidities and concomitant medication) may not resemble the patient treated in clinical practice who, at times, may have more severe, uncontrolled, or heavily-treated comorbidities.

It is important to underline a real aspect of treating patients with chronic HCV infection: managing the comorbidities and most importantly managing the treatment of these comorbidities to avoid significant DDIs.

Materials and Methods

We collected data on DDIs in the real-life treatment of chronically HCV-infected patients with the triple-DAA (3D) regimen containing ombitasvir/paritaprevir/ritonavir plus dasabuvir (AbbVie, North Chicago, IL, USA) with and without ribavirin in a compassionate study approved by the Romanian National Agency for Medicines and Medical Devices (study registration: 31315C/10.11.2014). For the DDI check the HEP-Drug Interaction Charts, University of Liverpool (UK), were used [7]. SPSS Statistics for Windows (version 22.0, IBM Corp, Armonk, NY, USA) was used for the statistical analysis. Data are presented as mean ± standard deviation (SD), when normally distributed and median (interquartile range: Q1, Q3) when abnormally distributed. For normally distributed variables, the independent-samples t test was used, with effect size calculation. For abnormally distributed variables non-parametric tests for independent samples were used. For categorical variables the Chi-square test was used. Statistical significance was established for p values below 0.05.

Results and Discussion

We have evaluated 44 patients with chronic hepatitis C and advanced fibrosis (cirrhosis), their mean ± SD baseline liver stiffness as determined by shear wave elastography being 17.7 ± 8.3 kPa. Patient characteristics are presented in Table I and Figure 1. Briefly, gender distribution was balanced (52.3% were males), the mean ± SD age was 57.3 ± 11.1 years, most patients had unfavourable IL-28B genotype (CT or TT in 89.5% of cases – Figure 1), and all had chronic infection with HCV genotype 1b. Sustained virological response was achieved by all patients (100% sustained virological response (SVR) rate), regardless of their comorbidities or the identified DDIs.

Table I

Patient characteristics

Characteristic	Mean ± SD	Median (Q1, Q3)
Age, years	57.3 ± 11.1	N/A
Duration of HCV evolution, years	10.4 ± 3.7	N/A
Liver stiffness*, kPa	17.7 ± 8.3	N/A

HCV – hepatitis C virus; SD – standard deviation. *Liver stiffness was evaluated by one trained operator through shear-waves elastography on Aixplorer (SuperSonic Imagine, Aix-en-Provence, France).

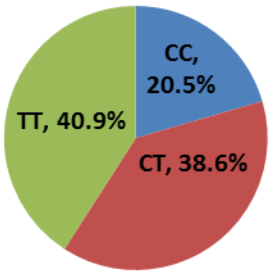

Figure 1.

Distribution of IL28-B polymorphism in the study group

Out of 44 patients only 14 (31.8%) did not declare any relevant comorbidities and 19 (43.2% – Figure 2) did not have concomitant medications (Figure 3, Table II).

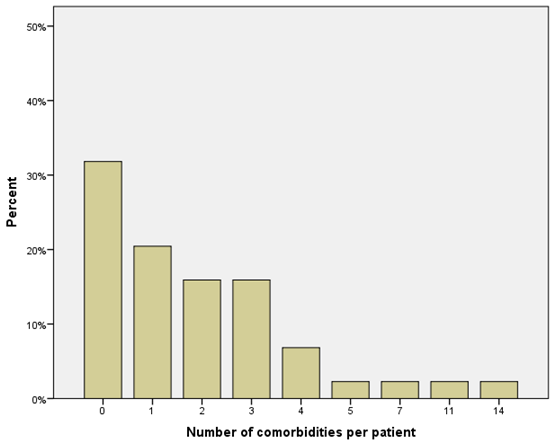

Figure 2.

Number of comorbidities per patient

The proportion of patients with comorbidities was not significantly different between genders (17/21, 81% in females *vs.* 13/23, 56.5% in males, p = 0.078, $\chi(1) = 3.020$). Similar results were recorded for the

proportion of patients with concomitant medication: 15/21, 71.4% in females vs. 10/23, 43.5% in males, p = 0.076, $\chi(1) = 3.495$; DDIs: 11/15 (73.3%) in females and 8/10 (80%) in males, p = 1.000, $\chi(1) = 0.146$; and DDI action (p = 0.182, $\chi(3) = 2.083$). Overall, we identified DDIs in 19 patients (76% of those receiving concomitant medication).

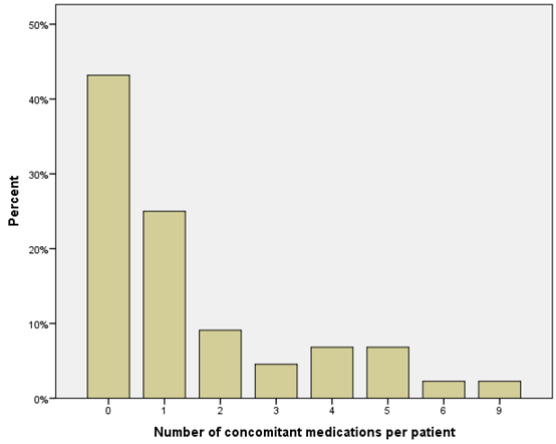

Figure 3.
Number of concurrent drugs per patient

Table II
Actions taken for managing or avoiding drug-drug interactions (DDIs) in the study population

Management of DDIs (n = 25)	**n (%)**
Close monitoring (concomitant medication unchanged)	14 (56)
Dose adjustment for concomitant medication	6 (24)
Treatment change for concomitant medication	3 (12)
Stop concomitant medication	2 (8)

At the mean age of 57.3 years old, our patients received treatment for different comorbidities, with a median of 2 (1, 4) comorbidities per patient, as follows: 14 patients were on treatment for arterial hypertension and 6 for portal hypertension; 3 patients had dyslipidaemia but only one of them was on current treatment with rosuvastatin (potential DDI); 6 patients had diabetes and 5 of them were receiving treatment, 2 with insulin (no DDI), and 3 with oral antidiabetic agents (no or potential DDIs); 4 women were receiving treatment for hypothyroidism with different doses of levothyroxine (potential DDI). Notably, more than half of the patients had a history of depressive syndrome in the past 3 years, and 7 of them were on actual antidepressant treatment at their screening visit, but most discontinued treatment after a specialty consult. Only 2 of the patients continued treatment as per specialist recommendation, one with bromazepam (no DDI) and the other with lorazepam (potential DDI – managed by close monitoring). Seven female patients were receiving treatment for osteopenia, one with vitamin D (no DDI information available) and the others with Osteocalcin® (over-the-counter supplement containing *Equiseti herba pulvis*, *Panacis radix pulvis*, coral calcium and other ingredients, for which no DDI information was available). Following endocrine evaluation, Osteocalcin® was stopped and vitamin D was continued. Notably, these specialist consults were undertaken prior to the DDI check, and only the final list of prescribed medication was considered "concomitant medication" during HCV treatment.

The patients included in the study received concomitant medication with an overall number of 29 different drugs. Table III presents the DDI check as provided through the HEP-Drug Interaction Charts [7]. Of these 29 drugs only one (3.4% – lercanidipine) associated a significant risk of DDI, and 11 associated potential DDIs and no DDIs, respectively (37.9% each). For 6 (20.7%) drugs no DDI information was available; of these, two were over-the-counter herbal supplements, administered for osteoporosis (Osteocalcin®) and diabetes (GlucoCare®), respectively; both were stopped during treatment of HCV infection.

As a result of the DDI check, 14 (56%) of the 25 patients taking concomitant medication did not require any intervention apart from close monitoring. Six patients (24%) required a dose adjustment for their concomitant medication, in 3 cases (12%) the concomitant medication was changed and in 2 cases (8%) the concomitant medication was stopped during HCV treatment, after assessment of the risk/benefit ratio. As there is currently no approved dose adjustment for the 3D treatment regimen, any necessary change was implemented for the concomitant medication.

We identified significantly higher baseline liver fibrosis in patients with comorbidities (mean difference 5.4 kPa, p = 0.036, t(36) = -2.178) and in those requiring concomitant medication (mean difference 7.6 kPa, p = 0.001, t(36) = -3.548). Baseline liver fibrosis was significantly higher in patients who required a change in concomitant medication compared with those who did not require any action for DDI (42.8 kPa *vs.* 15.5 kPa, p = 0.001, t(12) = -4.703, large effect size, d = 6.9); however, no statistical significance was recorded for age (p = 0.322, $r_s = 0.165$) or duration of HCV evolution (p = 0.798, $r_s = -0.043$). Baseline liver fibrosis was also significantly higher in patients who required concomitant medication change or stop compared with those who did not require any action or required only dose change (30.7 kPa *vs.* 15.4 kPa, p = 0.001, t(19) = 0.402 large effect size, d = 1.8).

Table III

Drug-drug interactions (DDIs) for concomitant medications

		No DDI	Potential DDI	Major DDI
Arterial hypertension/ heart failure	Metoprolol	X		
	Nebivolol	X		
	Amlodipine		X	
	Lercanidipine			X
	Indapamide		X	
	Candesartan		X	
	Valsartan		X	
	Perindopril	X		
	Trimetazidine	No information available		
Portal hypertension	Propranolol		X	
Dyslipidemia	Rosuvastatin		X	
Diabetes	Insulin	X		
	Metformin	X		
	Gliclazide		X	
	Glimepiride	X		
	GlucoCare®	No information available		
Hypothyroidism	Levothyroxine		X	
Depressive syndrome	Bromazepam	X		
	Lorazepam		X	
Osteopenia	Vitamin D	No information available		
	Osteocalcin®	No information available		
Other comorbidities	Methylprednisolone		X	
	Aspirin	X		
	Clopidogrel		X	
	Potassium	X		
	Magnesium	No information available		
	Betahistine	No information available		
	Ursodeoxycholic acid	X		
	Ginkgo biloba	X		

In the table are provided DDIs as provided through the HEP-Drug Interaction Charts, University of Liverpool (UK) [7].

IL28-B was statistically associated with the action required for DDI management ($p = 0.004$, $\chi(6) = 19.322$): patients with unchanged concomitant medication displayed mostly CT (8/14, 57.1%) and TT (6/16, 42.9%) genotypes; patients requiring dose change had TT (4/6, 66.7%) and CT (2.6, 33.3%) genotypes; patients requiring concomitant medication change were mostly CC (2/3, 66.7%) and TT (1/3, 33.3%) and those requiring stopping of concomitant medication were all (2/2) TT. However, these results might be biased due to the fact that significantly more patients with TT genotype had more comorbidities (15/18, 83.3% compared with CT: 12/17, 70.6% and CC: 3/9, 33.3%, $p = 0.030$, $\chi(2) = 6.988$) and they also accounted for more cases of concomitant medication to start with (13/18, 72.2%), compared with CT (10/17, 58.8%) or CC (2/9, 22.2%) genotypes ($p = 0.046$, $\chi(2) = 6.159$). Interestingly, although concomitant medication was administered more often in patients with TT genotype, DDIs were identified more often in patients with CC genotype (2/2, 100%), compared with CT (7/10, 70%) or TT (10/13, 76.9%), but these differences were not statistically significant ($p = 0.659$, $\chi(2) = 0.835$).

Accountability of ongoing medication is a must in patients scheduled to start DAA treatment for chronic HCV infection. Although the duration of antiviral treatment is relatively short (12 weeks), it is important to check for potential DDIs, as uncontrolled interactions may compromise the efficacy of the antivirals on the one hand and may put the patient at risk for toxicity or under-treatment of comorbidities on the other hand.

In our study, we requested specialty consults for cardiology, psychiatry, and endocrinology, and in a relatively high number of cases the consults indicated that there is no further need for continuation of the current medication. After reassessing the necessary treatment of comorbidities, the DDI profile was reviewed for all 44 patients and concomitant medications were adjusted according to indications, most patients (56%) requiring only close monitoring during co-administration.

Even if 12 weeks seem to be a short period of treatment, in this time frame 4 (9.1%) of our patients had an influenza episode that needed hospitalization and oseltamivir treatment. As no DDIs are reported for this co-administration, treatment was allowed and all patients recovered

from the flu episode without any consequences. Importantly, for cirrhotic patients who receive concomitant medication for comorbidities and who might need emergency therapy for different episodes of acute illness during the 12 weeks of therapy, DDIs should be checked each time, as pharmacokinetics are influenced not only by the metabolism patterns, but also by the total number of drugs received.

In our experience, the 3D regimen was generally well-tolerated, and its DDI profile was above expectations, particularly since the NS3/4A serine protease inhibitor paritaprevir is boosted with ritonavir (through inhibition of CYP3A4), and any concomitant medication metabolized through this cytochrome would be expected to generate DDIs.

We identified one major interaction with lercanidipine, a substrate of CYP3A4 [5]; due to the risk of increased exposure to lercanidipine, co-administration with the 3D regimen is contraindicated; the concomitant drug was stopped and the cardiology treatment regimen was adjusted accordingly. Potential interactions were also identified for other antihypertensive agents [6]. Co-administration of amlodipine has been reported to result in a 2.6-fold increase in its area under the curve and therefore the dose was reduced to 50%, as recommended in the drug's summary of product characteristics (SPC), with close clinical monitoring. Indapamide is a substrate of CYPs 2C9, 2D6 and also 3A4 and because of potential exposure increase with co-administration, its lowest possible dose was administered; the dose was determined through a consultation with each patient's cardiologist, and was dependent on the initial starting dose, the drug formulation, and the history of blood pressure dynamics. Candesartan and valsartan, both substrates of OATP1B1 [11], may also display increased exposure when co-administered with paritaprevir and ritonavir; dose reduction, along with close monitoring of blood pressure and heart rate, was recommended.

In six cases, propranolol, a substrate of CYP2D6 [8], was administered for portal hypertension and prevention of oesophageal varices bleeding; a potential DDI was identified, but data showed that co-administration does not require dose adjustment, and that close monitoring of blood pressure and heart rate may be sufficient.

Statins in general are notorious for their marked potential for DDIs. Rosuvastatin is a substrate of CYP2C9, CYP3A4 and OATPs 1B1, 1B3 and 1A2. Co-administration with the 3D regimen increases rosuvastatin exposure and the European SPC recommends a maximum daily dose no higher than 5 mg.

Among the drugs administered for treatment of diabetes, most did not associate DDIs, i.e., insulin is metabolized by hydrolysis and therefore there is little to no potential interaction; glimepiride (a substrate of CYP2C9) and metformin are considered DDI-free for the 3D regimen, but for gliclazide a potential DDI was recorded; it is a substrate of CYP2C9 and CYP2C19 and similar to glimepiride no interaction is expected for CYP2C9, but through interactions in CYP2C19, a 40% - 50% decrease in exposure to gliclazide is possible, and therefore serum glucose levels need to be monitored closely to determine whether an increased dose would be necessary.

Levothyroxine exposure may increase when co-administered with the 3D regimen through UGT1A1 inhibition, and the potential DDI should be managed by repeated assessments of thyroid stimulating hormone (TSH) levels and, potentially, by dose decrease. In 3 of our 4 patients on levothyroxine, the dose was reduced during co-administration.

Lorazepam exposure may increase when co-administered with the 3D regimen, and a dose reduction might be necessary; in our patient, the initial dose was continued, with close monitoring and good tolerability.

Dose reduction was also warranted for methyl-prednisolone (a substrate of CYP3A4 and P-gp). The management of clopidogrel was more complicated however, because it is converted to its active metabolite *via* multiple cytochromes: 3A4, 2B6, 2C19 and 1A2 and ritonavir induces CYP2C19 while inhibiting CYP3A4. However, a decreased exposure to the active metabolite has been reported, with subsequent non-responsiveness and the need to administer a different agent.

To our knowledge, this is the first study to assess DDIs in the treatment of chronic hepatitis C with DAAs in Romania, and the second article published internationally [4]. Our results are somewhat encouraging, as other authors report potentially significant DDIs in 66.3% of patients treated with the 3D regimen [4], compared to 44% in our study.

Interestingly, we have identified a statistically significant association between advanced baseline fibrosis and the need for changing concomitant medication ($p = 0.001$, large effect size, $d = 6.9$), potentially explained by the association of baseline fibrosis with the overall presence of comorbidities ($p = 0.036$) and concomitant medication ($p = 0.001$). The need for treatment adjustment in patients with cirrhosis has been described in the field literature, but through its association with hepatic impairment [1], and this was not the case in our study group, despite their advanced liver fibrosis [9], as all patients had apparently normal liver function.

A novel observation in our study was that IL28-B was statistically associated with the action required for DDI management ($p = 0.004$), with the TT genotype being associated more frequently with dose change (66.7% of patients had TT genotype),

treatment change (33.3% TT) and stopping of concomitant medication altogether (100% TT). This finding is neither confirmed nor refuted by the field literature, as no other similar studies have been performed to date, to our knowledge, but a recognized limitation of our study and a potential source of bias resided in the fact that significantly more patients with TT genotype had comorbidities ($p = 0.030$) and accounted for more concomitant medication compared with the other IL28-B genotypes ($p = 0.046$).

Conclusions

The 3D regimen displayed a good DDI profile in real-life settings, but close monitoring and accountability of concomitant medications should be performed by all treating physicians. DDI tools such as the HEP-Drug Interaction Charts from the University of Liverpool, UK, prove to be extremely useful, as they not only provide indication on the type of DDI (no clinically significant DDI, potential DDI, major DDI contraindicating co-administration), but also present the mechanism behind each interaction while providing pre-emptive guidance in accordance with European and US current guidelines.

Acknowledgement

AbbVie provided the 3D regimen in a compassionate study approved by the Romanian National Agency for Medicines and Medical Devices (study registration: 31315C/10.11.2014). AbbVie had no role in data interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

Conflicts of interest

ASC, OS, DM and MAS have been sub-investigators in AbbVie clinical trials. LLP and Adrian SC have been principal investigators in AbbVie clinical trials. ASC, LLP, OS, and Adrian SC have been speakers for AbbVie.

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