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Clinical management of drug–drug interactions in HCV therapy: Challenges and solutions

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Summary

Hepatitis C virus (HCV) infected patients often take multiple co-medications to treat adverse events related to HCV therapy, or to manage other co-morbidities. Drug–drug interactions associated with this polypharmacy are relatively new to the field of HCV pharmacotherapy. With the advent of the direct-acting antivirals telaprevir and boceprevir, which are both substrates and inhibitors of the cytochrome P450 (CYP) 3A iso-enzyme, knowledge and awareness of drug–drug interactions have become a cornerstone in the evaluation of patients starting and continuing HCV combination therapy. In our opinion, an overview of conducted drug–drug interaction studies and a list of contraindicated medications is not enough for the clinical management of these drug–drug interactions. Knowledge of pharmacokinetic profiles and concentration–effect relationships is key for the interpretation of these data, and insight into how to manage these interactions (e.g., dose adjustments, safe alternatives and therapeutic drug monitoring) is of equal importance. This review provides a practical overview of the safe and effective management of these clinical challenges.

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Introduction

With the introduction of the direct-acting antivirals (DAAs) telaprevir and boceprevir in Europe, US and other countries in 2011–2012, the management of drug–drug interactions in the treatment of patients with hepatitis C virus (HCV) has gained wide interest. Drug–drug interactions were not entirely new to the field, as certain combinations of ribavirin and human immunodeficiency virus (HIV) nucleoside analogues had been shown to be problematic before [1], and transplant hepatologists have long learned to consider drug–drug interactions with ciclosporin and tacrolimus. The current attention on drug–drug interactions and their clinical management, however, is unprecedented in hepatology and many other disease areas, and can only be compared to the introduction of HIV-protease inhibitors in the mid-90s.

Key Points

- With the advent of the direct-acting antivirals telaprevir and boceprevir, knowledge and awareness of drug-drug interactions have become a cornerstone in the evaluation of patients starting and continuing HCV combination therapy. This review aims to provide solutions for the safe management of these clinical challenges

Keywords: Drug interactions; Hepatitis C virus infection; Boceprevir; Telaprevir; Pharmacokinetics.
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Abbreviations: HCV, hepatitis C virus; DAAs, direct-acting antivirals; HIV, human immunodeficiency virus; SPCs, summary of product characteristics; Peg, polyethylene glycol; BID, twice daily; AKR, aldo-ketoreductases; P-gp, P-glycoprotein; AUC, area under the plasma concentration *vs.* time curve; FDA, Food and Drug Administration; EMA, European Medicines Agency; TDM, therapeutic drug monitoring; CYP, cytochrome P450; ECG, electrocardiogram; UGT, UDP-glucuronosyltransferase; ACE, angiotensin converting enzyme; AT1, angiotensin II receptor; PDE5, phosphodiesterase type 5; BOC, boceprevir; TVR, telaprevir; RBV, ribavirin; IFN, interferon.

Table 1. Overview of drug interactions with frequently used co-medications in HCV-infected patients. (See below-mentioned references for further information.)

Interacting agent	Anti-HCV agent	CI	Management (M) Alternative (A)	[Ref.]
Alfusozin (ALF)	BOC, TVR	Y		
Alprazolam (ALP)	BOC, TVR		M: monitor for toxicity ALP A: oxazepam	[23]
Amiodarone (AMI)	BOC		M: monitor for toxicity AMI	
	TVR	Y		
Amlodipine (AML)	TVR		M: monitor for toxicity AML; start with 5 mg of AML A: BOC	[24]
Atorvastatin (ATO)	TVR	Y	A: pravastatin	[24]
	BOC		M: monitor for toxicity ATO, maximum of 20 mg ATO/day A: pravastatin	[25]
Azathioprin (AZA)	RBV	Y		
Bosentan (BOS)	BOC, TVR		M: monitor for toxicity BOS	
Budesonide (BUD) inhalation, intranasally	BOC, TVR	Y	A: beclomethasone	
Carbamazepin (CAR)	BOC, TVR	Y	A: valproic acid, lamotrigine, levetiracetam	
Ciclosporin (CIC)	TVR		M: reduce CIC dose and/or extend dose interval; monitor CIC levels A: boceprevir and monitor CIC levels	[11, 12]
Clarithromycin (CLA)	BOC, TVR		M: monitor for toxicity CLA and TVR A: azithromycine	
Colchicine (COL)	BOC, TVR		M: monitor for toxicity COL; reduce dose of COL, see product label HCV PI	
Dabigatran (DAB)	TVR		M: monitor for toxicity DAB	
Dexamethasone (DEX)	BOC, TVR		M: monitor for efficacy HCV PI	
Digoxin (DIG)	TVR		M: monitor for toxicity DIG; start with low dose and monitor DIG levels	[22]
	BOC		M: monitor DIG levels	[27]
Diltiazem (DIL)	BOC, TVR		M: monitor for toxicity DIL A: low-dose amlodipine	
Disopyramide (DIS)	TVR	Y		
Domperidone (DOM)	BOC, TVR	Y	A: metoclopramide	
Drosperinone (DRO)	BOC	Y		
Ergotamin (ERG)	BOC, TVR	Y		
Erythromycin (ERY)	BOC, TVR		M: monitor for toxicity ERY and TVR A: azithromycine	
Escitalopram (ESC)	TVR		M: monitor for efficacy ESC, increase ESC dose if needed A: BOC	[21]
Ethinylestradiol (EE)	BOC, TVR	Y	M: use two non-hormonal types of contraception	[28]
Felodipine (FEL)	BOC, TVR		M: monitor for toxicity FEL A: low-dose amlodipine	
Flecainide (FLE)	BOC, TVR		M: monitor for toxicity FLE	
Fluticasone (FLU) inhalation, intranasally	BOC, TVR	Y	A: beclamethasone	
Halofantrin (HAL)	BOC, TVR	Y		
Ibutilide (IBU)	TVR	Y		
Imatinib (IMT)	BOC, TVR	Y		
Itraconazole (ITR)	BOC, TVR		M: monitor for toxicity ITR and HCV PI; maximum of 200 mg ITR/day A: fluconazole	
Ketoconazole (KET)	BOC, TVR		M: monitor for toxicity KET and HCV PI; maximum 200 mg KET/day A: fluconazole	[15]
Lidocain (LID), IV	BOC, TVR		M: monitor for toxicity LID	
Lumefantrin (LUM)	BOC, TVR	Y		
Methadone (MET)	BOC, TVR		M: monitor for efficacy MET	[17]
	IFN		M: monitor for toxicity MET	[29]
Methylprednisolone (MPR)	BOC, TVR	Y		
Midazolam (MID), PO	BOC, TVR	Y	A: temazepam or lorazepam or parenteral midazolam	[22, 2]

(*continued on next page*)

Table 1 (*continued*)

Interacting agent	Anti-HCV agent	CI	Management (M) Alternative (A)	[Ref.]
Midazolam (MID), IV	BOC, TVR		M: reduce IV dose with 50%	[22]
Nicardipine (NIC)	BOC, TVR		M: monitor for toxicity NIC A: low-dose amlodipine	
Nifedipine (NIF)	BOC, TVR		M: monitor for toxicity NIF A: low-dose amlodipine	
Nisoldipine (NIS)	BOC, TVR		M: monitor for toxicity NIS A: low-dose amlodipine	
Phenobarbital (PHB)	BOC, TVR	Y	A: valproic acid, lamotrigine, levetiracetam	
Phenytoine (PHT)	BOC, TVR	Y	A: valproic acid, lamotrigine, levetiracetam	
Pimozide (PIM)	BOC, TVR	Y		
Propafenon (PRF)	BOC, TVR		M: monitor for toxicity PRF	
Posaconazole (POS)	BOC, TVR		M: monitor for toxicity HCV PI A: fluconazol	
Prednisone (PRE)	BOC, TVR	Y		
Quinidine (QID)	BOC		M: monitor for toxicity QID	
	TVR	Y		
Rifabutin (RFB)	BOC, TVR	Y		
Rifampin (RIF)	BOC, TVR	Y		[15]
Salmeterol (SAL)	BOC, TVR	Y	A: formoterol	
Sildenafil (SIL)	BOC, TVR		M: maximum of 25 mg SIL/48 h	
Simvastatine (SIM)	BOC, TVR	Y	A: pravastatin or BOC with low-dose atorvastatin	
Sirolimus (SIR)	BOC, TVR	Y		
Sorafenib (SOR)	BOC, TVR	Y		
Sotalol (SOT)	TVR	Y		
St John's Wort (SJW)	BOC, TVR	Y		
Sunitinib (SUT)	BOC, TVR	Y		
Tacrolimus (TAC)	TVR	Y		[11]
	BOC		M: reduce TAC dose and/or extend dose interval; monitor TAC levels A: ciclosporin	[12]
Tadalafil (TAD)	BOC, TVR		M: maximum of 10 mg TAD/72 h	
Telbivudine (TEL)	IFN	Y		
Telithromycine (TEL)	BOC, TVR		M: monitor for toxicity TEL and TVR A: azithromycine	
Theophyllin (THE)	IFN		M: monitor for toxicity THE, monitor THE levels	
Trazodone (TRA)	BOC, TVR		M: monitor for toxicity TRA, start with low-dose TRA	
Triazolam (TRI)	BOC, TVR	Y	A: temazepam of lorazepam	
Vardenafil (VAR)	TVR		M: maximum of 2.5 mg VAR/72 h	
	BOC		M: maximum of 2.5 mg VAR/24 h	
Verapamil (VER)	BOC, TVR		M: monitor for toxicity VER A: low-dose amlodipine	
Voriconazole (VOR)	TVR	Y		
	BOC		M: monitor for toxicity BOC and VOR A: fluconazole	
Warfarin (WAR)	BOC, TVR		M: monitor for toxicity and efficacy WAR; monitor INR	
Zolpidem (ZOL)	TVR		M: monitor for efficacy ZOL	[23]

CI, contraindicated; BOC, boceprevir; TVR, telaprevir; RBV, ribavirin; IFN, interferon; IV, intravenous; HCV PI, hepatitis C virus protease inhibitor; INR, international normalized ratio; Y, yes.

Each health professional involved with HCV treatment (hepatologist, infectious disease specialist, nurse specialist, clinical pharmacist, etc.) will need a sound and complete understanding of the potential of a drug–drug interaction in every patient treated for HCV infection. This is a rapidly evolving field and many questions on specific drug combinations remain unanswered. Most of the drug–drug interaction studies are initially presented at conferences and many do not appear in peer-reviewed literature. Besides knowledge on potential mechanisms that form the basis of the development of drug–drug interactions, one should also have an overview of the most frequently occurring or most serious potential drug combinations. Finally, awareness of how to find reliable and up-to-date information is essential.

One of the reliable and up-to-date sources is a website from the University of Liverpool: www.hep-druginteractions.org. However, since only a small number of interactions have been

studied, one of the challenges is to provide expert opinion on potential interactions based on metabolic data and an understanding of the mechanisms. Currently, the website does not always provide information on effective alternatives when faced with a problematic interaction, and this would be a useful addition.

In this paper, we will review drug interactions with HCV agents and a number of therapeutic groups. As (potential) drug interactions between HIV and HCV drugs are extensive [2], it was decided that this deserves a separate review and, therefore, this will not be included here. Also, alternative and complementary medicines (e.g., herbals) may cause drug interactions but have not yet been studied and are consequently not the scope of this paper. Before discussion of potential drug interactions with anti-HCV agents, the pharmacokinetic properties of the drugs and current knowledge of their concentration–effect relationships will be discussed. This basic knowledge is required for an adequate interpretation of drug interaction data. It is important to remember that drug–drug interactions can be bidirectional, i.e., both drugs are affected.

Data on drug interactions were extracted from published literature, Summaries of Product Characteristics (SPCs) [3,4], abstract books from medical conferences, and clinical experience. If possible, a safe alternative is given to manage a specific drug interaction although it should be noted that clinical experience is limited. Data have been updated until July 1, 2012 and this overview is restricted to licensed anti-HCV agents.

Pharmacokinetics of anti-HCV agents

This paragraph focuses on the currently available anti-HCV agents ribavirin, polyethylene glycol (Peg)-interferon alfa, telaprevir and boceprevir. Ribavirin is a nucleoside analogue and as such a prodrug requiring intracellular activation to a triphosphate. Ribavirin-triphosphate accumulates in red blood cells because these cells lack the enzyme to degrade the triphosphate. Ribavirin has a bioavailability of approximately 64%, which is largely dependent on simultaneous intake of food. Absorption is dose-limited, so it is recommended to take ribavirin twice-daily (BID), although based on its long elimination half-life (approximately 300 h) less frequent dosing might have been more logical. Ribavirin is not metabolised by hepatic enzymes and does not influence hepatic metabolism of other agents. It is eliminated unchanged by the kidneys.

Interferon alfa is a recombinant representative of a natural protein that can only be administered parenterally; its pharmacokinetic profile is improved by encapsulation of the molecule in a peg "coat". As a result, dosing frequency could be reduced to once-weekly subcutaneous administration. There are 2 forms marketed: 2a and 2b, which have limited pharmacokinetic differences, and in this paper interferon alfa is meant to represent both 2a and 2b products. Peg-interferon alfa is not a substrate of hepatic metabolism and does not show a direct inducing or inhibitory effect on hepatic metabolism of other agents.

Boceprevir and telaprevir are both orally available HCV protease inhibitors with food-dependent absorption and relatively short elimination half-lives, necessitating three times daily administration (BID administration of telaprevir is currently in phase III clinical trial). Both agents are substrates of CYP3A, although for boceprevir this is not the primary route of metabolism; boceprevir is primarily metabolised by aldo–ketoreductases (AKR) and only a minor proportion is subject to CYP3A-mediated metabolism [5]. Both boceprevir and telaprevir are substrates of the membrane transporter P-glycoprotein (P-gp), which is present at many sites, including the gastro-intestinal tract, blood–brain barrier, placenta; P-gp is a so-called efflux pump and prevents uptake of substrates, and as such can be seen as a protection of the body against noxious substances. Telaprevir and boceprevir are both strong inhibitors of CYP3A, with telaprevir being associated with a stronger inhibitory effect than boceprevir (see data on immunosuppressants and midazolam below). Both agents also appear to be inhibitors of P-gp (again, with boceprevir being a weaker inhibitor than telaprevir, based on digoxin data), but it should be noted that this is more difficult to assess as a large overlap between CYP3A and P-gp substrates exists. Both agents are so-called mechanism-based inhibitors of CYP3A, which means that CYP3A is inactivated. As a consequence, reduced CYP3A activity is maintained even when telaprevir or boceprevir use is discontinued, until new CYP3A enzymes are generated (approximately 1 week).

Based on the above, much attention will be directed to interactions between boceprevir/telaprevir on one hand and CYP3A/P-gp substrates/inhibitors/inducers on the other hand.

Concentration, effect relationships

It is difficult to interpret results from drug–drug interaction studies without a detailed insight into concentration–response relationships. If there is no change in plasma concentrations when drug A is added to drug B, one can easily conclude that both agents can be safely combined from a pharmacokinetic perspective. But what changes in drug concentrations is generally accepted to be related to reduced efficacy: −30%,−50% or −70%? At which elevated drug concentration is the risk for toxicity significantly increased? Which pharmacokinetic parameter is most closely associated with therapeutic response and thus should be used for interpretation: the average exposure to the drug during one dose interval (area-under-the-concentration *vs.* time curve, AUC), or for instance the trough concentration (C_{min})? A sensible statement can only be made if a concentration–effect relationship is known, there is some idea of a target concentration, how far away the "average" patient is from this putative threshold and how large the interpatient variability is in pharmacokinetics. It is not surprising that in clinical practice such a well-balanced and thorough evaluation of drug interaction data is hardly possible, and inevitably we have to look at drug interaction data outcomes in a more general way. Regulatory bodies such as the Food and Drug Administration (FDA) or European Medicines Agency (EMA) could decide that any reduction in exposure of more than a certain percentage (i.e., 30%, 40%, 50%) could be defined as clinically relevant, and hence any combination of drugs that leads to this kind of plasma drug concentration change should lead to either a dose adjustment or a contraindication. Such a general condition can then be applied to agents with comparable mechanisms of action and pharmacokinetic properties. This is, however, difficult to justify given differences in concentration, effect relationships and is currently not an FDA or EMA viewpoint.

Another important consideration is that in pharmacokinetic studies, plasma (or serum) pharmacokinetic parameters are assessed, while it is known that anti-HCV agents are primarily

active inside the hepatocyte and not in plasma. Hepatocytes, however, do not represent an easily accessible biological matrix. Animal data may not always reflect the human situation, as there are differences in expression of uptake transporters between species [6]. As a result, we tend to assume that globally, there is a correlation between concentrations at the site of activity and in plasma, and hence changes in plasma concentrations will result in more or less similar changes inside the hepatocyte. For all DAAs, correlations have been found between plasma concentrations and HCV RNA decline after the start of treatment [7,8]. Thus, the assumption that plasma concentrations are a surrogate for levels inside the hepatocyte appears valid so far. However, in individual patients, there could be a "mismatch" between plasma and hepatocyte concentrations, for instance caused by genetic polymorphisms in uptake or efflux transporters present on the cell membrane of a hepatocyte. Another example of a mismatch could be for nucleoside analogues that are activated intracellularly to triphosphates: plasma concentrations of the parent compound may not always be related to intracellular concentrations of the triphosphate.

A further important aspect is the possibility to use therapeutic drug monitoring (TDM) to assess the presence of a clinically relevant drug interaction. TDM can play a major role in the management of a drug–drug interaction and to evaluate the effectiveness of an intervention such as a dose adjustment. For anti-HCV agents, this is currently only possible for ribavirin in a number of specialized laboratories. Literature suggests that steady-state plasma concentrations of ribavirin at week 8 or later should be 2.0 mg/L or higher to reduce the risk of virological failure as much as possible [9]. If a drug interaction with ribavirin is known or suspected, this may lead to changes in ribavirin plasma concentrations and TDM can then be recommended. TDM is also possible, and probably indispensible, for a number of therapeutic groups that are influenced by HCV protease inhibitors, such as immunosuppressants and antiretroviral agents. But also in other situations the *adagium* "one dose does not fit all" can be advocated to understand whether a drug interaction is causing inter- or intrapatient variability in drug concentrations. Currently, TDM of HCV protease inhibitors telaprevir and boceprevir is not yet possible because of practical issues around blood sampling, storage of samples, limited availability of pure compounds, etc. In addition, TDM comes at a cost and tends only to be performed in specialist centers.

Immunosuppressive agents (including steroids)

Without doubt one of the most important drug interactions with the currently available anti-HCV agents are those with immunosuppressants, such as tacrolimus and ciclosporin [10]. These immunosuppressants are substrates of both CYP3A and P-gp and, with the above-described inhibitory effects of boceprevir and telaprevir on CYP3A and P-gp, it was expected that the plasma concentrations of the immunosuppressants would be largely increased. In particular, the interaction between tacrolimus and telaprevir has a magnitude that is unprecedented in clinical pharmacology: the AUC of tacrolimus is increased by 70.3-fold and this combination would be lethal if doses are not adjusted [11]. Ciclosporin levels are increased "only" 4.1-fold when combined with telaprevir. Also for boceprevir, the interaction with tacrolimus is stronger than for ciclosporin, but differences are less pronounced than for telaprevir: tacrolimus levels increase 17-fold and ciclosporin levels 2.6-fold when combined with boceprevir [12]. Less attention has been paid to the effects of the immunosuppressants on the levels of the HCV protease inhibitors, but no influence is expected.

The above-mentioned data have been collected in healthy volunteers; preliminary data presented at EASL 2012 suggest that with TDM of immunosuppressants directly from the start of combined treatment these combinations are indeed manageable with adjusted doses that appear to be around 50% of the observed differences in healthy volunteers [13]. Overall, the ciclosporin dose needed to be adjusted by an average factor of 1.3 while the interaction study in healthy volunteers showed a 2.6-fold increase. However, in this study, patients were admitted to hospital for correction of drug dosing and intensively monitored. Phase II studies are ongoing that might allow less intensive monitoring and more flexible dosing of the immunosuppressants, for instance a very low dose of tacrolimus taken once-a-week when combined with telaprevir. At the current time, there is some uncertainty whether the safety and efficacy of tacrolimus once weekly (with telaprevir) can be extrapolated from daily use of tacrolimus (without telaprevir), even when similar target trough levels of tacrolimus are achieved. The combination of ciclosporin and boceprevir causes the smallest interaction and could be considered a preferred option. There are no data on the use of other immunosuppressants such as sirolimus and everolimus, but it is expected that the effects are similar to those with tacrolimus.

Systemically applied corticosteroids such as prednisone and methylprednisolone are CYP3A substrates and higher steroid levels may occur when combined with telaprevir and boceprevir, and this is not recommended. This also holds true for corticosteroids that are locally applied by inhalation or intranasally such as budesonide and fluticasone: Cushing syndrome may occur with DAAs. Regarding the systemic glucocorticoid dexamethasone, this agent can act as an enzyme inducer and may be associated with *low* DAA levels. There are data available suggesting that beclomethasone can be used safely in patients on strong CYP3A inhibitors [14] and consequently this could be the corticosteroid of choice for patients on HCV protease inhibitors. Dermatically applied steroids are not expected to cause significant systemic absorption; this could be different for anorectal administration to treat anorectal discomfort.

Antimicrobial agents (non-HIV)

Ketoconazole is a prototype CYP3A inhibitor often used during clinical development of putative CYP3A substrates such as telaprevir and boceprevir to investigate interactions. It has been shown that telaprevir levels were increased by 62% and also ketoconazole levels were elevated by 46–125%, demonstrating telaprevir's CYP3A/P-gp inhibitory potential [15]. It is recommended that telaprevir can de dosed normally, but that the ketoconazole dose should not exceed 200 mg/day to avoid development of toxicity. This recommendation has been extended to itraconazole although the combination with telaprevir was not formally studied. For boceprevir and ketoconazole, similar effects have been noticed. Consequently maximum doses of ketoconazole and itraconazole of 200 mg/day are also in the product label for boceprevir.

Besides ketoconazole, the macrolide clarithromycin is a well-known CYP3A inhibitor. Plasma concentrations of boceprevir were only marginally increased (+21%) during co-administration and, therefore, these agents can be safely combined without dose adjustments [16]. Telaprevir has not been tested with clarithromycin, but a similar recommendation can be given. The potential increase in clarithromycin levels, however, warrants electrocardiogram (ECG) monitoring in patients also on telaprevir, as QT prolongation may occur. Where possible, azithromycin is an alternative to clarithromycin, as the former macrolide is not a CYP3A inhibitor or substrate.

Rifampin is the prototype of a strong enzyme inducer and is often difficult to combine with CYP substrates such as telaprevir and boceprevir. The AUC of telaprevir in combination with rifampin was reduced by 92% when compared to telaprevir alone, and this combination is contraindicated [15]. Boceprevir has not been tested with rifampin, but a contraindication also applies.

Methadone/buprenorphine

Because (former or current) intravenous drug use is a major transmission route for HCV, a considerable number of patients who are receiving opiate substitution therapy and/or actively using illicit drugs will be considered for therapy with DAAs. Hence there is a risk for a drug–drug interaction. Methadone is commonly used in opiate substitution programs and has been extensively studied. Telaprevir reduced methadone levels on average by 29%, but this effect is most probably attributed to displacement of methadone from plasma protein-binding sites [17]. Free, active concentrations of methadone remained largely unchanged. A somewhat smaller decrease in methadone levels was seen with boceprevir: AUC and C_{max} were reduced by 22% and 15%, respectively; free methadone levels were not reported [18]. Surprisingly, the use of peg-interferon alfa appeared to cause a small increase in methadone levels of about 15%, which is unlikely to be associated with the need for a dose reduction to prevent methadone toxicity. Taking these apparently opposite effects of telaprevir/boceprevir and peg-interferon alfa together, close monitoring might be prudent in patients on methadone, when HCV combination therapy is initiated. Importantly, there should be a low threshold for methadone dose adjustment based on patient responses. In some centers, patients and their friends who are being considered for antiviral therapy are provided with opiate antagonists (naloxone), along with instructions for their use and this may be a prudent precaution in individuals with erratic consumption of illicit opiates.

Buprenorphine is an alternative to methadone for patients with opiate addiction. It has multiple metabolic pathways, including CYP3A, so an increase in plasma concentrations was possible when combined with CYP3A inhibitors such as telaprevir or boceprevir. However, buprenorphine levels were not increased when this was combined with telaprevir and also no signs of toxicity were observed [19]. Boceprevir caused a minor increase in buprenorphine AUC (+19%) which was associated with a 45% decrease in the AUC of norbuprenorphine, demonstrating an effect of boceprevir on this CYP3A pathway [18]. These changes, however, are not considered clinically relevant.

Buprenorphine is also available in a fixed-dose combination with naloxone. Systemic bioavailability of oral naloxone is very low (<3%) due to extensive first-pass metabolism (mainly UDP-glucuronosyltransferase (UGT) and partly CYP3A). Boceprevir increased naloxone AUC by 33%, suggesting that bioavailability of naloxone is somewhat improved when these agents are co-administered [18].

Antidepressants

It is generally accepted that the use of peg-interferon alfa can lead to psychiatric disorders including depression. Concomitant use of antidepressants with HCV treatment will thus not be a rarity and this poses the risk for a drug–drug interaction with DAAs, as both groups are CYP substrates. Escitalopram has been studied for the prevention of peg-interferon-induced depression and was, therefore, a logical candidate to be tested for a drug interaction with HCV protease inhibitors. With telaprevir, no change occurred in telaprevir levels, but escitalopram levels were decreased by an average of 35% [20]. When initiating escitalopram in a patient on telaprevir, one should dose titrate high enough before concluding that the antidepressant is not effective. The effect of boceprevir on escitalopram had the same direction as with telaprevir, although the magnitude of the decrease in AUC was smaller (−17%) [21].

It is unlikely that all patients can be effectively treated with escitalopram, and clinicians may have preferences for other antidepressants based on personal experience. Some of these agents (e.g., sertraline and mirtazepine) are CYP3A substrates and increased plasma concentrations of the antidepressant may occur when combined with telaprevir or boceprevir. Other antidepressants are more selectively metabolised by CYP2D6 (e.g., paroxetine, duloxetine and fluoxetine) and their pharmacokinetics are expected not to be influenced by telaprevir and boceprevir as the latter agents do not possess CYP2D6 inhibitory activity. More research is needed in this area.

Sedatives

A number of benzodiazepines are heavily dependent on CYP3A for their metabolism and interactions with boceprevir and telaprevir can be expected. Midazolam is a prototype CYP3A substrate, but is also relevant here as it is being used as premedication before endoscopy or gastroscopy. The AUC of oral midazolam was increased 9-fold with telaprevir [22] and 5.3-fold with boceprevir [2] and, therefore, oral midazolam is contraindicated with both DAAs. The magnitude of an interaction with *parenteral* midazolam is less than that observed with oral midazolam, as the inhibition of presystemic CYP3A metabolism is no longer relevant. Indeed, midazolam AUC increased only 3.4-fold when i.v. midazolam was added to telaprevir (*vs.* 9-fold with oral midazolam, see above) and there was no change in C_{max} of midazolam [22]. Administration of 50% of the normal parenteral dose in patients on boceprevir or telaprevir is probably safe.

Other oral benzodiazepines such as triazolam and alprazolam [23] are contraindicated. Zolpidem levels were reduced by approximately 50% with steady-state telaprevir, so possibly a higher dose of zolpidem is needed [23]. Ketamine is extensively metabolised in the liver by various CYP enzymes and consequently, if CYP3A is involved, there are potentially multiple escape pathways. Propofol is mainly eliminated renally and, therefore, no interaction with DAAs is expected.

Statins

Most statins are also CYP3A substrates and, not surprisingly, CYP3A inhibitors such as telaprevir and boceprevir are expected to increase statin levels and the associated risk of severe toxicity such as rhabdomyolysis. Indeed, atorvastatin levels were elevated almost eight times with telaprevir [24]. This combination is a contra-indication, as is simvastatin, which has not been tested. The effect of boceprevir on atorvastatin was less strong: statin levels increased 2.3 times and this interaction appears to be manageable by starting with a low dose of atorvastatin (10 mg) [25]. An alternative option might be pravastatin as this statin is not a CYP substrate. Pravastatin levels were marginally increased when combined with boceprevir (1.5-fold), probably caused by inhibition of the organic anion-transporting polypeptide (OATP) 1B1 [25,26]. There are no data on rosuvastatin and HCV protease inhibitors.

Some clinicians have the opinion that, given the relatively short treatment duration with DAAs, at least with telaprevir (12 weeks), one can also temporarily stop the statin to avoid toxicity associated with a potential drug–drug interaction.

Cardiovascular agents (other than statins)

Calcium entry blockers are known CYP3A (and partly also P-gp) substrates and thus increased exposure can be expected with CYP3A inhibitors such as telaprevir and boceprevir. This was also observed: amlodipine levels increased 1.8-fold when combined with telaprevir [24]. It is advised to start with a low dose of amlodipine (5 mg) and titrate to the desired effect. Effects of telaprevir on other calcium channel blockers are expected to be more severe than this, since most of these agents have a larger CYP3A-mediated first-pass effect. Thus, telaprevir can cause a more pronounced drug interaction. There are currently no data on boceprevir and amlodipine, but as boceprevir is also known as a CYP3A inhibitor (though weaker than telaprevir) a similar recommendation as with telaprevir appears logical.

Some of the calcium entry blockers have very low systemic bioavailability (4–8%: barnidipine, lacidipine, lercanidipine) due to extensive first-pass metabolism. However, when combined with CYP3A inhibitors, such as telaprevir or boceprevir, systemic exposure may easily increase several-fold; therefore, these agents should not be used as a first choice.

Diuretics, angiotensin converting enzyme inhibitors (ACE) and angiotensin II receptor antagonists (AT1) are all classes of agents without extensive CYP metabolism, and hence combination with telaprevir and boceprevir is not expected to be problematic. β-receptor blocking agents are also not expected to cause problems as they are mainly eliminated renally (e.g., atenolol and sotalol) or metabolised through CYP2D6 (e.g., metoprolol and carvedilol). Anti-arrhythmics have a narrow therapeutic window and some are CYP3A substrates (e.g., amiodarone and bepridil). These are contraindicated with the strong CYP3A inhibitor telaprevir and caution is warranted with the moderate CYP3A inhibitor boceprevir.

Digoxin has been tested with telaprevir [22] and boceprevir [27] as a prototype P-gp substrate: digoxin levels were increased by 85% with telaprevir so this DAA can be defined as a moderate P-gp inhibitor and one should start with a low-dose digoxin in a patient on telaprevir. With boceprevir, the impact on digoxin levels was less than with telaprevir: AUC and C_{max} of digoxin were increased by 19% and 18%, respectively. This suggests that boceprevir is a very mild P-gp inhibitor.

Antidiabetics

Use of antidiabetics should be monitored carefully in patients with hepatic impairment to avoid the occurrence of severe hypoglycaemia. Repaglinide is one of the few oral antidiabetics that is partially metabolised by CYP3A and theoretically could interact with the CYP3A inhibitors boceprevir and telaprevir. Repaglinide's primary route of metabolism, however, is CYP2C8. This would be the escape pathway in the presence of a CYP3A inhibitor; therefore, no interaction with DAAs through this mechanism is expected. Repaglinide is also a substrate for OATP transporters and may consequently interact with DAAs in a non-CYP mediated mechanism. Some other oral antidiabetics are also metabolised by the liver, but not the CYP3A iso-enzyme. For instance, glimepiride is a CYP2C9 substrate, but this enzyme is not influenced by boceprevir [26] or telaprevir. Metformin is not expected to cause a problem when combined with DAAs.

Other agents

Finally, in this paragraph some agents are described that did not fall in one of the main therapeutic areas that are listed above. This includes either agents that have been tested or those with a contraindication based on theoretical considerations.

Plasma concentrations or the estrogen component of oral contraceptives are reduced by about 25–30% when combined with boceprevir [16] or telaprevir [28], and it is recommended to take additional (non-hormonal) precautions to prevent pregnancy. This is not only based on the observed drug interaction data, but also because HCV therapy includes ribavirin, which is teratogenic. Therefore, pregnancy should also be avoided from that important perspective.

The following agents are contraindicated with telaprevir and boceprevir because these agents are strongly dependent on CYP3A for metabolism and have a narrow therapeutic range: alfusozin, cisapride, ergotamin and derivates and pimozide.

Colchicine is another CYP3A substrate with a narrow therapeutic range; the drug labels contain a dosing algorithm for combined use of DAAs with colchicine, depending on its indication.

Besides rifampin, other strong enzyme inducers are carbamazepine, phenytoin, phenobarbital and St John's wort; these inducers should not be combined with DAAs to avoid the occurrence of subtherapeutic levels of DAAs. Alternative anti-epileptic agents, such as valproic acid, levetiracetam and lamotrigine, are not enzyme inducers or CYP3A substrates. Therefore, they should be easier to combine with DAAs.

Phosphodiesterase type 5 inhibitor (PDE5) inhibitors such as sildenafil and tadalafil are CYP3A substrates and toxic levels can occur when combined with telaprevir or boceprevir. When these agents are applied at high doses for treatment of pulmonary hypertension, they are contraindicated with DAAs. However, for their use in erectile dysfunction, lower doses and/or less frequent dosing should be safe: sildenafil, 25 mg per 48 h; tadalafil, 10 mg per 72 h; vardenafil, 2.5 mg per 24 h (boceprevir) or 2.5 mg per 72 h (telaprevir). The proton pump inhibitor esomeprazole does not influence telaprevir exposure. Ibuprofen and

diflunisal analgesic agents are interesting in this perspective as they are known to be AKR inhibitors, and AKR is responsible for part of boceprevir's metabolism. A drug–drug interaction study, however, did not show an effect of diflunisal or ibuprofen on boceprevir pharmacokinetics [4].

An overview of the drug interactions with frequently used co-medications in HCV-infected patients is shown in Table 1.

Limitations of current drug interaction data

Many of the above-mentioned drug–drug interaction studies have been performed in healthy volunteers to avoid potential harm to patients who are at risk for toxicity or subtherapeutic effects when potentially interacting drugs are combined. This assumes that the effect of a certain drug–drug interaction is similar in healthy subjects as in an HCV-infected patient. This might not always be the case. For instance, HCV-infected patients with cirrhosis may also have impaired CYP450 capacity and have higher plasma concentrations of CYP450 substrates than healthy subjects. Theoretically, this would mean that they are at even more risk for drug toxicity when a drug–drug interaction occurs that is based on CYP450 inhibition, but at lower risk for subtherapeutic effects when a drug–drug interaction is based on enzyme induction, impaired absorption, etc. Nevertheless, extrapolation from healthy subjects to patients is still considered to be the norm, although in individual cases therapeutic drug monitoring, if available, might be helpful to assess the clinical relevance for that specific patient.

Conclusions

This overview illustrates that drug–drug interactions are an important and potentially frequent problem when using DAAs in clinical practice. It also shows, however, that many of the interactions are manageable by either dose adjustments or selecting a safe alternative, but only if one has sufficient knowledge and expertise to deal with these pharmacokinetic issues. The aim of this review was to provide this insight, as well as to raise awareness that drug–drug interactions in modern HCV treatment may have unwanted effects, such as increased toxicity or lack of therapeutic effect. This is of course most likely to have an impact on patients on multiple medications and/or treated by multiple physicians. Whenever one doubts about the safety of a certain combination, one should consult a pharmacist or clinical pharmacologist.

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