HHS Public Access

Author manuscript

Nat Rev Gastroenterol Hepatol. Author manuscript; available in PMC 2015 November 05.

Published in final edited form as:

Nat Rev Gastroenterol Hepatol. 2013 October ; 10(10): 596–606. doi:10.1038/nrgastro.2013.106.

Drug–drug interactions during antiviral therapy for chronic hepatitis C

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Abstract

The emergence of direct-acting antiviral agents (DAAs) for HCV infection represents a major advance in treatment. The NS3 protease inhibitors, boceprevir and telaprevir, were the first DAAs to receive regulatory approval. When combined with PEG-IFN and ribavirin, these agents increase rates of sustained virologic response in HCV genotype 1 to ~70%. However, this treatment regimen is associated with several toxicities. In addition, both boceprevir and telaprevir are substrates for and inhibitors of the drug transporter P-glycoprotein and the cytochrome P450 enzyme 3A4 and are, therefore, prone to clinically relevant drug interactions. Several new DAAs for HCV are in late stages of clinical development and are likely to be approved in the near future. These include the protease inhibitors, simeprevir and faldaprevir, the NS5A inhibitor, daclatasvir, and the nucleotide polymerase inhibitor, sofosbuvir. Herein, we review the clinical pharmacology and drug interactions of boceprevir, telaprevir and these investigational DAAs. Although boceprevir and telaprevir are involved in many interactions, these interactions are manageable if health-care providers proactively identify and adjust treatments. Emerging DAAs seem to have a reduced potential for drug interactions, which will facilitate their use in the treatment of HCV.

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Competing interests

J. J. Kiser declares associations with the following companies: Bristol-Myers Squibb, Janssen, Merck, Vertex. J. R. Burton Jr declares associations with the following companies: Abbvie, Gilead, Vertex. G. T. Everson declares associations with the following companies: Abbott, Amgen, Biotest, Bristol-Myers Squibb, Centocor, Eisai, Gilead, GlaxoSmithKline, GlobeImmune, HepQuant LLC, Janssen-Tibotec, Kadmon, Medtronic, Merck, Novartis, Ortho Biotech, Pfizer, Pharmassett, Roche-Genentech, Schering-Plough, Source, Vertex. See the article online for full details of the relationships.

Author contributions

All authors researched data for the article, wrote the article, made substantial contributions to discussion of content, and reviewed/edited the manuscript before submission.

Introduction

Worldwide, ~150 million people are living with chronic HCV infection.[1] Without treatment, two-thirds of HCV-infected individuals will develop chronic liver disease and many will progress to cirrhosis and hepatocellular carcinoma.[1] These complications can be prevented with antiviral treatment, but not all patients are eligible for, able to access, tolerate, or respond to current therapies. Thus, new agents are desperately needed. Fortunately, multiple agents are in various stages of clinical development for the treatment of HCV.

Compounds that target each of the proteins encoded by the single-stranded HCV RNA genome include inhibitors of three structural proteins (core, E1 and E2), the ion channel protein p7, and six nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B).[2] Boceprevir and telaprevir, NS3 protease inhibitors, were the first direct-acting antiviral agents (DAAs) to receive regulatory approval for the treatment of HCV. These drugs are specific for HCV genotype 1, which is the most common genotype in the world, but also the most difficult to treat.[3] So-called triple therapy—that is, PEG-IFN plus ribavirin plus either boceprevir or telaprevir—has increased cure rates (sustained virologic response; SVR) by roughly 30% in both treatment-naive and treatment-experienced patients with HCV genotype 1.[4–9] However, there is still room for improvement. Multiple contraindications and toxicities are associated with PEG-IFN plus ribavirin, and with triple therapy. Boceprevir and telaprevir can cause anaemia and gastrointestinal effects. Boceprevir causes a bitter, earthy, or metallic taste[10] and telaprevir can cause rash (even severe or life-threatening rash) and anorectal discomfort.[11] Both are substrates and inhibitors of the cytochrome P450 3A (CYP3A) enzyme and several drug transporters, which predisposes them to drug–drug interactions.

Emerging DAAs will probably overcome many of the shortcomings of current therapies. The next wave of DAAs will include two new NS3 protease inhibitors, simeprevir and faldaprevir; the NS5A inhibitor daclatasvir; and the nucleotide NS5B polymerase inhibitor, sofosbuvir. In some cases, these agents will be added to PEG-IFN plus ribavirin therapy in much the same way as boceprevir and telaprevir, but others, such as sofosbuvir, might be approved in an interferon-free regimen. Subsequent advances will see the emergence of additional DAAs and novel combinations ultimately leading to a new treatment standard of interferon-free multi-DAA treatment, with or without ribavirin. Studies suggest SVR rates of ~80–90% in treatment-naive patients when faldaprevir, simeprevir, daclatasvir or sofosbuvir are added to PEG-IFN plus ribavirin combination therapy.[12-15] Several all-oral DAA combinations are showing similarly high SVR rates in phase II studies.[16-18] Addition of two or more DAAs to PEG-IFN plus ribavirin provides almost 100% SVR even in historically difficult-to-treat patient populations.[19-21] These studies suggest new treatments will certainly increase SVR rates. Many new DAAs also have longer half-lives than current therapies, which facilitates less frequent dosing that should enhance compliance. For instance, faldaprevir, simeprevir, daclatasvir and sofosbuvir are all being given once daily in phase III studies. Most investigational agents seem to offer improved genotype coverage, and also seem to have fewer adverse effects. Available data suggest investigational DAAs might also have a reduced potential for drug–drug interactions. However, several of these agents are substrates of CYP3A and drug transporters and some inhibit and induce enzymes

and transporters, implying that potential drug–drug interactions will remain an important aspect of management into the foreseeable future.

In this Review, we describe the principles and clinical consequences of drug interactions in patients with chronic HCV, summarize the pharmacology and drug interaction potential of boceprevir, telaprevir and the investigational DAAs faldaprevir, simeprevir, daclatasvir and sofosbuvir, and examine the magnitude and management of specific drug–drug interactions with these agents.

Principles of drug interactions

Drug–drug interactions can be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic drug interactions result in a change in drug concentrations. Pharmacodynamic drug interactions do not result in a change in drug concentrations, but can result in additive, synergistic or antagonistic effects. For instance, in the treatment of HCV, two drugs that both cause anaemia would be considered to have a pharmacodynamic interaction. The focus of this Review is on potential pharmacokinetic interactions.

Pharmacokinetic drug interactions occur at the level of drug absorption, metabolism, distribution or elimination. In terms of interactions at the level of metabolism, the CYP enzymes are responsible for the breakdown of many drugs. Specifically, the CYP3A4 isoform metabolizes the majority of marketed medications.[22] CYP enzymes are capable of being induced and inhibited. Induction of CYP enzymes results in a reduction in concentrations of substrates; conversely, inhibition of CYP enzymes results in an increase in concentrations of substrates. CYP enzymes are not the only site of drug–drug interactions however. An increasing number of drug–drug interactions are attributed to membrane transporters. Unlike CYP enzymes, our understanding of membrane transporters is in its infancy because analytical techniques to identify transporters were not available until the early 1990s. Although thousands of membrane transporters have been identified, only a few have been implicated in clinically relevant drug–drug interactions. Examples include P-glycoprotein (P-gp, also known as multidrug resistance protein 1), solute carrier organic anion transporter family member 1B1 (SLCO1B1, also known as organic anion transporting polypeptide 1B1 or OATP1B1), multidrug resistance-associated proteins (MRP), and ATP-binding cassette sub-family G member 2 (ABCG2, also known as breast cancer resistance protein or BCRP). As with the CYP enzymes, membrane transporters can be induced or inhibited.

For every drug, there exists of concentrations that balances the likelihood of efficacy with the probability of toxicity (Figure 1). For some drugs, this range of concentrations is wide, for others the range of concentrations is narrow. Many factors can affect drug concentrations, including organ dysfunction, body weight, diet, host genetics and, the topic of this Review, drug interactions. Drugs with a wide therapeutic range have a high tolerance to drug–drug interactions because concentration shifts are unlikely to increase the probability of toxicities or decrease the likelihood of efficacy. However, for drugs with a narrow therapeutic range, drug–drug interactions can have important clinical implications. Drug interactions that increase concentrations (for example, CYP or transporter inhibition)

can lead to an increase in concentration-dependent toxicities. Subtherapeutic concentrations can lead to the development of drug resistance, which can compromise the success of current and future treatments. Some antiviral drugs are considered to have a narrow therapeutic range, but whether boceprevir, telaprevir or investigational DAAs fall into this category is currently unclear.[23]

The potential for pharmacokinetic interactions between drugs is often tested first in healthy volunteers. This approach is logical considering the consequences of an interaction (that is, toxicity or viral resistance). However, additional pharmacokinetic considerations exist in people with HCV. First, HCV infection itself has been shown to impair drug metabolism by reducing microsomal enzymatic activity.[24] Second, CYP enzyme activity is impaired as liver disease progresses.[25] Furthermore, with increased fibrosis, a higher likelihood of portal-systemic shunting exists.[26] Thus, the magnitude of a drug interaction could differ in individuals with HCV based on the degree of hepatic impairment or stage of fibrosis, and might be particularly problematic in those with advanced liver disease.

DAA pharmacology

Table 1 shows the pharmacology and interaction potential of current and late-phase investigational agents for HCV. The pharmacology of boceprevir, telaprevir, simeprevir, faldaprevir, daclatasvir and sofosbuvir are described in greater detail below.

Protease inhibitors

Boceprevir, telaprevir, simeprevir and faldaprevir prevent the NS3 viral protease from cleaving the enzymes responsible for viral replication. Boceprevir and telaprevir are linear peptide mimetics with a ketoamide group that covalently binds with a serine in the catalytic triad.[27] Simeprevir and faldaprevir are noncovalent peptide mimetic inhibitors that have a macrocyclic structure.[27] All four protease inhibitors are metabolized by CYP3A, and are therefore affected by potent CYP3A inhibitors (for example, ketoconazole) and inducers (for example, rifampin). These HCV protease inhibitors also inhibit CYP3A, to varying degrees, and thus might increase concentrations of other CYP3A substrates. Ritonavir is an HIV protease inhibitor. However, in the field of HIV, it is no longer used for its antiviral effects, but is instead used for its ability to potently inhibit CYP3A. Ritonavir increases the concentrations of CYP3A substrates, reducing their dosing requirements and prolonging the dosing interval.[28] The concept of pharmacokinetic enhancement or ‘boosting’ of CYP3A substrates with ritonavir is now being used in the field of HCV. Two HCV protease inhibitors, danoprevir and ABT450, are being studied in combination with a boosting dose of ritonavir.[29,30]

Boceprevir

Boceprevir is administered at a dose of 800 mg every 7–9 h. Boceprevir exposures are increased by 65% with food, thus the drug should be taken with food, but bioavailability is similar regardless of dietary fat content. Omeprazole does not affect boceprevir absorption.[31] Boceprevir is metabolized by aldoketoreductase enzymes and CYP3A, and it is also a substrate for P-gp. Boceprevir is a moderate CYP3A inhibitor and a weak P-gp

inhibitor. *In vitro*, no evidence exists that boceprevir inhibits other CYP enzymes or induces any CYP enzymes. Boceprevir inhibits the drug transporters OATP1B1 and BCRP[32] and is 75% protein bound. After a single 400 mg dose of boceprevir (which is lower than the approved 800 mg dose), the area under the curve (AUC) and maximum concentration (C_{max}) of the active form of boceprevir (SCH534128) were increased 32% and 28%, respectively, in those with moderate hepatic impairment (Child–Pugh B) and 45% and 62%, respectively, in those with severe hepatic impairment (Child–Pugh C), relative to individuals with no impairment.[33] No dosage adjustment is necessary for patients with renal impairment.[33] Boceprevir AUC is only 10% lower in patients with end-stage renal disease requiring haemodialysis than in individuals with normal renal function.[33]

Telaprevir

The recommended dose of telaprevir is 750 mg every 7–9 h with a high (≥20g) fat meal, but telaprevir 1,125 mg twice daily dosing was noninferior to thrice daily dosing in a phase III trial.[34] Telaprevir is metabolized by CYP3A and is a strong CYP3A inhibitor and moderate P-gp inhibitor.[11] Telaprevir has been shown *in vitro* to inhibit several hepatic and renal transporters.[35] It is 59–76% protein bound. *In vitro*, telaprevir did not inhibit CYP enzymes other than CYP3A and has a low potential to induce CYP2C, CYP3A or CYP1A. Surprisingly, telaprevir AUC and C_{max} are reduced by 46% and 49%, respectively, in those with moderate (Child–Pugh B) hepatic impairment.[36] The mechanism for this finding is unclear, but could relate to decreased protein binding or reduced absorption. Thus, the appropriate dose of telaprevir in those with moderate or severe hepatic impairment has not been determined. The reduction in telaprevir AUC and C_{max} was less for those with Child–Pugh A hepatic impairment: 15% and 10%, respectively, so no dose adjustment is necessary in these patients. A single-dose study of telaprevir in individuals with creatinine clearances <30 ml/min/1.73 m^2 (equivalent to 0.50 ml/s/m^2) found a 10% higher C_{max} and 21% higher AUC than those without renal impairment, thus no dosage adjustment is necessary for those with mild, moderate, or severe renal impairment, but telaprevir has not been studied in persons with end-stage renal disease or those requiring haemodialysis.[11]

Simeprevir

Simeprevir is being evaluated at a dose of 150 mg once daily in phase III trials. Simeprevir is metabolized by CYP3A, and is a mild inhibitor of CYP3A and CYP1A2[37] as well as an inhibitor of OATP1B1 and MRP2.[38] In eight volunteers with Child–Pugh B cirrhosis, simeprevir AUC and C_{max} were increased 2.62-fold and 1.76-fold, respectively, compared with eight volunteers without hepatic impairment, but similar to those observed in persons with Child–Pugh A cirrhosis.[39] No data are available at this time on whether simeprevir needs to be taken with food or with a certain type of meal. The degree of protein binding is also unknown.

Faldaprevir

The highest faldaprevir dose being evaluated in phase III trials is 240 mg once daily. Faldaprevir does not alter caffeine (CYP1A2), efavirenz (CYP2B6), or dextromethorphan (CYP2D6) exposures, but oral midazolam was increased 2.92-fold and *S*-warfarin increased

1.29-fold, which suggests that faldaprevir moderately and weakly inhibits CYP3A and CYP2C9, respectively.[40] Faldaprevir inhibits uridine glucuronosyltransferase 1A1, which causes hyperbilirubinaemia.[41] Faldaprevir is a substrate for P-gp and MRP2.[42] Faldaprevir pharmacokinetics are not altered in patients with Child–Pugh A cirrhosis.[42] No data are currently available on food requirements or protein binding for faldaprevir.

NS5A inhibitors

Daclatasvir inhibits NS5A, a protein essential to the replication machinery of HCV and critical in the assembly of new infectious viral particles.[43] Daclatasvir is dosed at 60 mg once daily in phase III trials. Daclatasvir is a substrate for CYP3A and a substrate and inhibitor of P-gp;[44] the drug is 99% protein bound.[45] Daclatasvir did not have a clinically relevant effect on the CYP3A probe midazolam.[46] Dose adjustments of daclatasvir do not seem to be necessary in the setting of hepatic impairment.[47] Total daclatasvir plasma AUC and C_{max} are lower in patients with hepatic impairment than healthy controls, but unbound drug exposures are similar. Although studies are lacking, dose adjustment for renal impairment might not be needed owing to the mainly hepatic route of elimination of this agent. Food requirements for daclatasvir have not been reported.

Polymerase inhibitors

NS5B RNA-dependent RNA polymerase is essential for HCV replication as it catalyses the synthesis of the complementary minus-strand RNA and subsequent genomic plus-strand RNA.[48] Two types of polymerase inhibitors exist, nucleos(t)ide and non-nucleoside analogues. The nucleos(t)ide analogues are prodrugs, requiring activation by host phosphorylation enzymes for activity; the phosphorylated nucleos(t)ide drug competes with endogenous nucleotide bases for incorporation into replicating HCV. Sofosbuvir undergoes phosphorylation by host enzymes to a uridine triphosphate analogue, which is responsible for its antiviral effects; it is not metabolized by CYP enzymes.[49] Measuring the phosphorylated anabolite in hepatocytes would be challenging, thus the pharmacokinetic and interaction data available with sofosbuvir describe concentrations of sofosbuvir itself (that is, the prodrug) and the uridine metabolite in blood plasma (GS-331007) and might not necessarily reflect the active form of the drug. The recommended dose of sofosbuvir is 400 mg once daily. Dose adjustments of sofosbuvir are necessary in patients with renal impairment.[50] Sofosbuvir exposures are doubled in people with Child–Pugh B and C hepatic impairment, but GS-331007 concentrations are unchanged.[51] Interestingly, despite the increase in parent drug concentration and no change in metabolite concentrations, these HCV-infected individuals with cirrhosis (n = 16) had a 3.4-log reduction in HCV RNA after 7 days of sofosbuvir monotherapy versus the 4.7-log reduction observed in HCV-infected individuals without cirrhosis. This finding suggests that impaired phosphorylation or portal-systemic shunting could influence viral responses to this DAA. At this time, no data on food requirements or protein binding for sofosbuvir are available.

Specific drug interactions

In the era of DAAs, health-care providers involved in the treatment of patients with HCV must consider potential drug interactions between DAAs and other drugs and supplements.

Figure 2 provides an algorithm for screening, adjusting, and monitoring for potential drug interactions with DAAs. The following section is a summary of established and theoretical interactions of DAAs with other agents. We have highlighted those interactions that have been identified as clinically important or within therapeutic classes commonly used in people with HCV. New data are limited for interactions with antidepressants[52] and no new data are available for interactions with antipsychotics, anxiolytics, sleep aids and antihypertensive agents, thus the reader is referred to a prior review for interactions with these classes of drugs.[53] We also outlined in detail in a prior review the interaction potential of boceprevir and telaprevir with HMG-CoA reductase inhibitors (that is, statins), which are classic substrates for the transporter OATP1B1.[53]

Immunosuppressants

Ciclosporin and tacrolimus are CYP3A and P-gp substrates. Telaprevir and boceprevir are both inhibitors of CYP3A and P-gp, with telaprevir being a more potent inhibitor of both. The effects of boceprevir and telaprevir on ciclosporin and tacrolimus have been evaluated in healthy volunteers. Boceprevir increases ciclosporin and tacrolimus concentrations by 2.7-fold and 17.1-fold, respectively.[54] Telaprevir increases ciclosporin and tacrolimus concentrations by 4.64-fold and 70.3-fold, respectively.[55] Simeprevir seems to have a much smaller influence on ciclosporin and tacrolimus than either boceprevir or telaprevir. Ciclosporin and tacrolimus AUC are increased 19% and decreased 17%, respectively, by simeprevir.[56] Thus, doses of ciclosporin and tacrolimus do not require initial adjustment when administered with simeprevir, but immunosuppressant concentrations should be monitored during treatment. The decrease in tacrolimus, although small, might be magnified by clearance of HCV RNA, which further enhances metabolism and reduces trough levels of tacrolimus and can increase risk of allograft rejection.[57] Sofosbuvir does not affect ciclosporin or tacrolimus concentrations. Interestingly, ciclosporin increases sofosbuvir AUC 353%, but the uridine metabolite in blood plasma (GS-331007) is unchanged.[58] The mechanism and clinical importance of the increased sofosbuvir concentration is unknown. A healthy volunteer drug–drug interaction study has not been performed with DAAs and sirolimus, but one group reported a 24-fold higher sirolimus AUC than values previously reported in the literature when telaprevir was used to treat 16 patients with HCV after liver transplantation.[59]

Although telaprevir and boceprevir do not currently have regulatory approval in the post-transplant setting, these individuals are arguably the patients in greatest need of treatment. Several groups have reported their initial experience with PEG-IFN plus ribavirin in combination with telaprevir or boceprevir post-transplantation.[60–62] SVR data are limited at this time, but experts are forecasting a 50% cure rate[63] and a few trends have emerged. First, treatment of HCV post-transplantation is a major endeavour with our current therapies and should be undertaken only by experienced providers with appropriate infrastructure. Second, the interactions between immunosuppressants and boceprevir or telaprevir require vigilance from health-care providers and require resources, but do seem manageable. Third, toxicities are common, such as anaemia requiring blood transfusions and growth factors. Death, although rare, has occurred during this treatment.

Figure 3 summarizes our protocol at the University of Colorado Denver, USA, for using triple therapy in patients with recurrent HCV after liver transplantation. We use ciclosporin plus mycophenolate mofetil during HCV protease-inhibitor-based treatment. Therapeutic drug monitoring of ciclosporin is performed before, during and after protease inhibitor treatment to refine doses. During triple therapy, we utilize a 2 h post-dose ciclosporin level (C2) with a goal of C2 of approximately 500 ng/ml.[64] Telaprevir is preferentially used to minimize the time on the HCV protease inhibitor. Ciclosporin is preferentially used because of the smaller magnitude of the drug interactions with HCV protease inhibitors relative to tacrolimus or sirolimus and augmentation of the antiviral activity of HCV treatment.[63]

Antiretroviral drugs

Owing to shared routes of transmission, ~30% of people infected with HIV are co-infected with HCV.[65] A critical consideration in people with HIV–HCV co-infection is the potential for drug interactions. Many antiretroviral drugs are substrates for or otherwise affect CYP enzymes and drug transporters. Several drug–drug interaction studies have been performed with DAAs and antiretroviral agents in healthy volunteers. A limited number of antiretroviral agents seem to be safe to administer with telaprevir and boceprevir. Tenofovir disoproxil fumarate (TDF) is a frequently prescribed antiretroviral agent. Boceprevir does not alter tenofovir AUC.[66] Telaprevir increases tenofovir AUC by 30%.[67] In isolation, this finding is unlikely to have clinical relevance, but in combination with other agents that might increase tenofovir concentrations, renal function should be monitored. Raltegravir, an HIV integrase inhibitor, can be safely combined with both boceprevir and telaprevir.[67,68] In healthy volunteers, interactions occur between telaprevir and boceprevir and several ritonavir-boosted HIV protease inhibitors, whereby concentrations of both the HIV and HCV protease inhibitors are reduced.[67,69] The mechanism(s) for these interactions are unclear and the focus of current investigation. In the meantime, only the ritonavir-boosted HIV protease inhibitor, atazanavir, can be safely combined with telaprevir.[70] Ritonavir-boosted darunavir, fosamprenavir and lopinavir should not be used with telaprevir or boceprevir. Non-nucleoside reverse transcriptase inhibitors are primarily inducers of CYP3A enzymes, with efavirenz being the most potent inducer of the class. Efavirenz reduces the AUC of boceprevir and telaprevir by ~50% in healthy volunteers.[66,67] Telaprevir has been studied at a higher dose than usual (1,125 mg every 8 h) with efavirenz and this dose increase seems to overcome the inductive effects of efavirenz. Telaprevir AUC is reduced 16% by etravirine, but etravirine concentrations are unchanged.[71] By contrast, boceprevir is not substantially affected by etravirine, but boceprevir reduces etravirine AUC by 23%.[72] The AUC for rilpivirine is increased 79% by telaprevir[71] and 39% by boceprevir.[73] Telaprevir and boceprevir increase maraviroc AUC by 9.5-fold and 3-fold, respectively.[74] Thus, a reduced dose of maraviroc, 150 mg twice daily, should be used in combination with these protease inhibitors. A study with elvitegravir and cobicistat is underway.

The interaction potential with several antiretroviral agents and faldaprevir, daclatasvir, simeprevir and sofosbuvir has been explored. Faldaprevir has been studied with TDF, efavirenz and ritonavir-boosted darunavir.[75] Darunavir and tenofovir AUC were increased by 15% and 22%, respectively, when administered with faldaprevir. Faldaprevir AUC was

increased by 130% with ritonavir-boosted darunavir, decreased by 22% with TDF and decreased by 35% with efavirenz. In this phase III trial, patients co-infected with HIV and HCV taking ritonavir-boosted darunavir received faldaprevir 120 mg daily and those taking efavirenz received faldaprevir 240 mg daily.[75] Daclatasvir has been studied with TDF, efavirenz and ritonavir-boosted atazanavir. The daclatasvir dose should be increased from 60 mg to 90 mg daily when combined with efavirenz and decreased to 30 mg daily with ritonavir-boosted atazanavir.[76] Simeprevir has been studied with TDF, rilpivirine, efavirenz, raltegravir and ritonavir-boosted darunavir. Efavirenz reduced simeprevir exposure by 71% and co-administration is not advised. Ritonavir-boosted darunavir increased simeprevir exposure 2.6-fold, even after dose reduction of simeprevir from 150 mg to 50 mg; thus, co-administration of simeprevir with ritonavir-boosted protease inhibitors is not recommended.[77] Sofosbuvir has been studied with ritonavir-boosted darunavir, raltegravir, rilpivirine and the combination antiretroviral product containing TDF, emtricitabine and efavirenz.[78] After a single dose of sofosbuvir given before and 14 days after the antiretroviral agent(s), the pharmacokinetics of the antiretroviral compounds and sofosbuvir and its uridine metabolite in blood plasma were largely unchanged. Sofosbuvir seemed to decrease raltegravir AUC by 27% and increase tenofovir C_{max} by 25% (AUC was unchanged), whereas sofosbuvir increased ritonavir-boosted darunavir AUC by 34%.[78] The mechanisms and clinical importance (if any) of these interactions are unknown.

Table 2 provides a summary of available interaction data of DAAs and antiretroviral agents. In brief, telaprevir and boceprevir have many interactions with antiretroviral agents that might preclude safe combination. Simeprevir seems to have similar contraindications to telaprevir and boceprevir (that is, no addition of efavirenz or ritonavir-boosted protease inhibitors). The interactions of daclatasvir and faldaprevir with antiretroviral agents seem to be manageable with DAA dose modification. Sofosbuvir has the most benign interaction profile of the DAAs studied with antiretroviral agents to date, with the caveat that data regarding the active form of the drug (that is, the uridine analogue triphosphate) has not been reported.

Oral contraceptives

Ribavirin is teratogenic. Thus, prevention of pregnancy is of paramount importance during ribavirin-based HCV treatment. Boceprevir and telaprevir reduce ethinyl oestradiol AUC by 26% and 28%, respectively.[79,80] Boceprevir and telaprevir reduce norethindrone AUC by 4% and 11%, respectively.[79,80] With telaprevir, the reductions in oral contraceptive exposures affected serum gonadotropin concentrations, suggesting loss of contraceptive efficacy.[80] However, this phenomenon was not observed for boceprevir.[79] Despite the lack of effect of boceprevir on norethindrone pharmacokinetics, drosperinone AUC is doubled by boceprevir.[66] Thus, this progestin should be avoided due to the potential for hyperkalaemia and increased likelihood of progestin-related adverse effects. Ethinyl oestradiol and norethindrone were increased by 12% and 15%, respectively, by simeprevir.[81] Daclatasvir did not alter the concentrations of ethinyl oestradiol or norgestimate.[44] Faldaprevir increases ethinyl oestradiol and levonorgestrel AUC by 40%.[42] Thus, oral contraceptive efficacy might be compromised with boceprevir and telaprevir, but not with simeprevir, faldaprevir, or daclatasvir. Data for sofosbuvir are not yet available.

Phosphodiesterase inhibitors

No formal drug interaction studies have been undertaken with DAAs and phosphodiesterase inhibitors, but the HIV protease inhibitor ritonavir has been shown to markedly increase exposures to phosphodiesterase inhibitors. Sildenafil AUC is increased 11-fold with ritonavir 500 mg twice daily,[82] vardenafil AUC is increased 49-fold with ritonavir 600 mg twice daily[83] and tadalafil AUC is increased 2.2-fold with ritonavir 200 mg twice daily.[84] On the basis of these interactions, phosphodiesterase inhibitors when used for pulmonary arterial hypertension, should not be used with boceprevir and telaprevir. When used for erectile dysfunction, phosphodiesterase inhibitor doses and dosing frequencies should not exceed the following with the HCV protease inhibitor owing to the theoretical potential for increased exposures: sildenafil 25 mg every 48 h, vardenafil 2.5 mg every 24 h, and tadalafil 10 mg every 72 h.

Corticosteroids

Systemic steroids can be used in patients post-transplantation or in those with autoimmune hepatitis. Systemic steroids have not been studied with telaprevir. With boceprevir, prednisone and prednisolone AUC were increased by 22% and 37%, respectively, after a single 40 mg dose of oral prednisone. Thus, dose adjustments of systemic prednisone are probably unnecessary with boceprevir.[85] Inhaled and intranasal corticosteroid use has been associated with secondary adrenal insufficiency in the setting of HIV protease inhibitors. Due to inhibition of CYP3A, the exposures of exogenous corticosteroids are increased with subsequent inhibition of endogenous cortisol. Fluticasone is the corticosteroid that has been implicated in the majority of adrenal insufficiency reports in HIV-infected persons on HIV protease inhibitors. This agent, along with budesonide,[86] should be used with caution in the setting of DAAs that inhibit CYP3A. Inhaled or intranasal beclomethasone and flunisolide are possible alternatives,[87] although both agents require investigation in the setting of DAA treatment of HCV.

Opioids and opioid replacement

Oxycodone, tramadol and fentanyl are primarily metabolized by CYP3A,[88] and thus might require dose reduction when used with boceprevir or telaprevir. Other opioids have a reduced potential for interaction with boceprevir, telaprevir, simeprevir, faldaprevir, daclatasvir and sofosbuvir. Hydrocodone and codeine are metabolized by CYP2D6.[88] Morphine, hydromorphone and oxymorphone are glucuronidated by uridine glucuronosyltransferase 2B7.[88] Individuals with a history of substance abuse might be receiving opioid replacements. Methadone and buprenorphine do not inhibit or induce CYP enzymes, but their pharmacokinetics and pharmacodynamics can be affected by drugs that do affect CYP enzymes.[89,90] Telaprevir displaces methadone from its plasma protein binding sites, which causes a reduction in total drug concentrations, but concentrations of the unbound (free) form of the drug are unchanged. Thus, a methadone dose adjustment is probably unnecessary with the addition of telaprevir.[91] Telaprevir has no effect on buprenorphine pharmacokinetics.[92] Boceprevir reduces R-methadone AUC by 15% and increases buprenorphine AUC by 19%.[93] These changes are small and unlikely to require

opioid replacement dose adjustment. Methadone pharmacokinetics are unaffected by simeprevir[94] and sofosbuvir.[95]

Foods, dietary and herbal supplements

Grapefruit juice has been implicated in several clinically important drug interactions, including with tacrolimus and ciclosporin.[96] Two constituents of grapefruit juice, the furanocoumarins and flavonoids, have been associated with inhibition of intestinal CYP3A and inhibition of drug transporters, respectively.[96] As boceprevir, telaprevir and some investigational DAA are substrates for CYP3A, P-gp and organic anionic transporting polypeptides, there is a theoretical potential for interactions with grapefruit juice. The likelihood and magnitude of an interaction with DAA would depend on several factors, including bioavailability of the DAA, the intrinsic level of expression of CYP3A4 or transporters in the gut, and the quantity and properties of the juice consumed. In the absence of formal interaction studies with DAA, a conservative approach would be to avoid consumption of grapefruit juice during DAA treatment.

Use of herbal supplements is common in patients with HCV.[97] Preliminary results of a survey presented in 2012 revealed that 64% of drug interactions identified in patients on telaprevir or boceprevir were with herbal supplements.[98] Unfortunately, no formal studies of the pharmacokinetics of DAAs when used in combination with herbal supplements have been undertaken. Top-selling herbal supplements include black cohosh, cranberry, *Echinacea*, garlic, *Ginkgo biloba*, ginseng, saw palmetto, silymarin (milk thistle), soy and St John's wort.[99] *In vitro*, *Echinacea*, garlic, ginkgo biloba, ginseng, silymarin, and St John's wort have been shown to inhibit or induce enzymes or transporters involved in the metabolism or disposition of boceprevir and telaprevir.[99] *In vivo*, Echinacea[100,101] and silymarin[102,103] do not substantially alter HIV protease inhibitor exposures, but garlic and ginseng reduce CYP3A substrates by 44–51%.[104,105] Reductions of a similar magnitude could result in subtherapeutic boceprevir or telaprevir exposures, thus use of garlic and ginseng supplements should be avoided. The potential influence of *Ginkgo biloba* on boceprevir or telaprevir is unclear. Midazolam AUC is reduced, but ritonavir-boosted lopinavir is unchanged with *Ginkgo biloba* co-administration.[106] In the absence of data for DAAs, this supplement should be used with caution. St John's wort is a potent inducer of enzymes and transporters, which has caused therapeutic failure of many drugs.[107] It is therefore contraindicated with boceprevir and telaprevir and should be avoided during antiviral treatment of HCV regardless of the specific DAA used.

Conclusions

Boceprevir and telaprevir represent major advances in the treatment of HCV, but they are unfortunately involved in a number of clinically important drug interactions; they are susceptible to the effects of potent inhibitors and inducers, but also capable of altering the pharmacokinetics of other drugs. The investigational DAAs simeprevir, faldaprevir and daclatasvir are CYP3A substrates and therefore might be altered by potent inhibitors and inducers, but they seem less likely to act as culprits in interactions. Sofosbuvir seems to have

a very low potential for drug interactions. Health-care providers must be vigilant about identifying and managing interactions with DAA to ensure therapeutic success.

Acknowledgements

J. J. Kiser acknowledges financial support from NIH grant R03 DK096121.

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Key points

- ■ Direct-acting antiviral agents (DAAs) represent a major advance in the treatment of chronic HCV infection
- ■ Boceprevir and telaprevir, the first DAAs to receive regulatory approval, are involved in many clinically important drug–drug interactions
- ■ Providers must proactively screen for potential drug–drug interactions with boceprevir and telaprevir before and during treatment and adjust therapies as needed
- ■ Many investigational DAAs have fewer, but are not devoid of, drug–drug interactions

Review criteria

A PubMed search was performed with the following search terms: “SCH503034”, “boceprevir”, “VX-950”, “telaprevir”, “TMC435”, “simeprevir”, “BI 201,335”, “faldaprevir”, “BMS-790,052”, “daclatasvir”, “GS-7,977”, “PSI-7,977” and “sofosbuvir”. English-language articles containing information related to pharmacokinetics, pharmacology, and/or drug interaction potential were reviewed. Conference abstracts were also searched from the International Workshop on Clinical Pharmacology of Hepatitis Therapy, Annual Meetings of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, and Conference on Retroviruses and Opportunistic Infections 2008–2012.

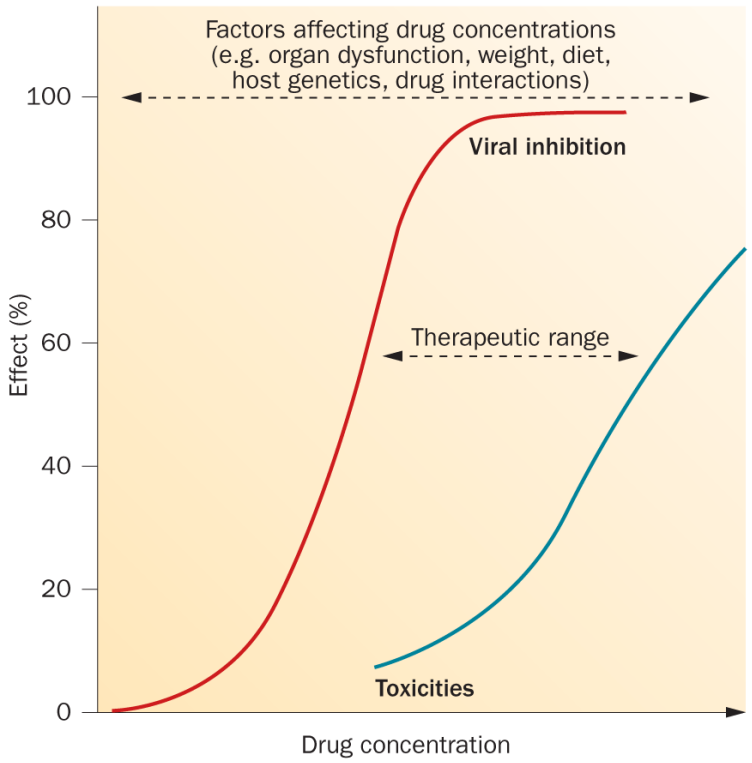

Figure 1.

Concept of a therapeutic range. For every drug, there exists a range of concentrations that balances the likelihood of efficacy with the probability of toxicity.

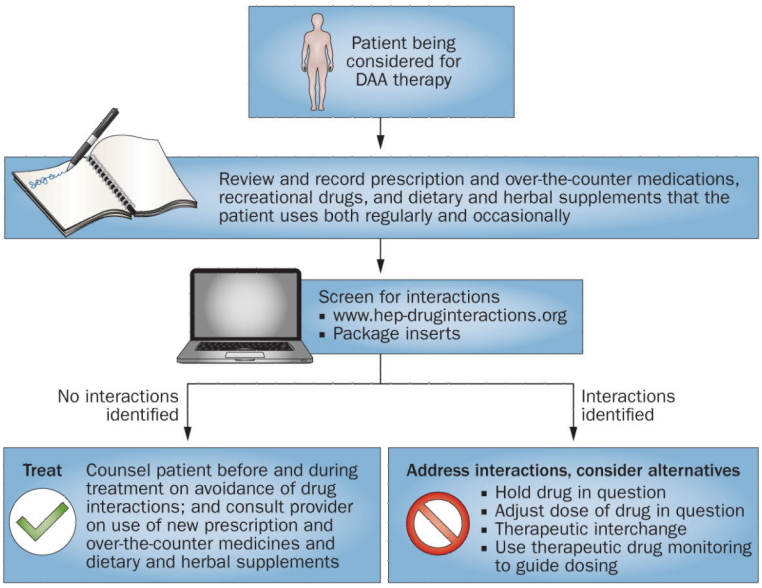

Figure 2.

An algorithm for screening, adjusting and monitoring for potential drug interactions with DAAs. Abbreviation: DAA, direct-acting antiviral.

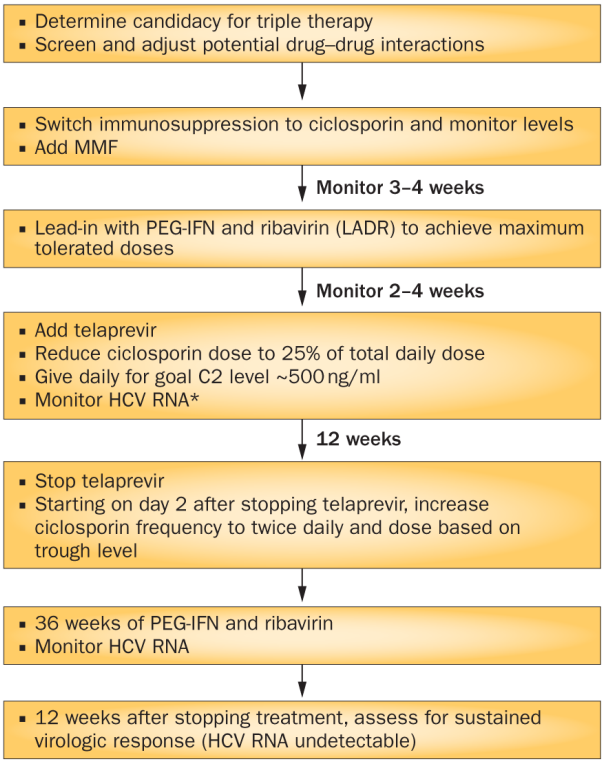

Figure 3.

Protocol for using triple therapy in patients with recurrent HCV after liver transplantation.

*All treatment discontinued if HCV RNA >1,000 IU/ml at 4–12 weeks of triple therapy with PEG-IFN-α, ribavirin and a protease inhibitor or detectable at/after 24 weeks.

Abbreviations: LADR, low accelerated dose regimen; MMF, mycophenolate mofetil.

Table 1

Pharmacology and interaction potential of currently approved and investigational DAAs in late-phase clinical development

Drugs	Route of metabolism or excretion	CYP effects	Transporter substrate	Transporter effects	Comments
Protease inhibitors					
ABT450/ ritonavir	CYP3A[108]	CYP3A inhibition by ritonavir	ND	Inhibits OATP1B1[109]	NA
Asunaprevir	ND	Moderate inhibitor of CYP2D6; weak inducer of CYP3A4[110]	OATP1B1/2B1[111]	Weak P-gp and OATP1B1/1B3[111] inhibitor	NA
Boceprevir[10]	CYP3A, AKR	Moderate CYP3A inhibitor	P-gp	Weak P-gp inhibitor[112]	NA
Danoprevir/ ritonavir	CYP3A	CYP3A inhibition by ritonavir	ND	ND	A study with midazolam (CYP3A probe) and warfarin (CYP2C9 probe) showed that danoprevir did not change the effect of ritonavir on these probes (midazolam increased, warfarin decreased)[113]
Faldaprevir	CYP3A	Moderate inhibitor of hepatic and intestinal CYP3A; weak inhibitor of CYP2C9;[40] inhibitor of UGT1A1[41]	P-gp, MRP2[42]	Inhibits OATP1B1, OATP1B3, OATP2B1[42]	NA
Simeprevir	CYP3A	Mild inhibitor of CYP1A2 and intestinal CYP3A[37]	ND	OATP1B1 and MRP2 inhibitor[38]	NA
Telaprevir[11]	CYP3A	Strong CYP3A inhibitor	P-gp	Moderate P-gp inhibitor	NA
NS5A inhibitors					
ABT267	ND	ND	ND	ND	AUC and C_{max} increased 62% and 67%, respectively, by ritonavir[114]
Daclatasvir	CYP3A[44]	ND	P-gp[44]	Moderate P-gp and OATP1B1 inhibitor[46]	NA
Ledipasvir[49]	ND	Not a CYP inhibitor or inducer	P-gp	Weak inhibitor of P-gp, BCRP, OATP1B1, OATP1B3	NA
Nucleos(t)ide polymerase inhibitors					
Mericitabine	Renal[115]	ND	ND	ND	Cytidine and uridine analogue
Sofosbuvir	Renal[50]	ND	P-gp	ND	Uridine analogue[116]

Drugs	Route of metabolism or excretion	CYP effects	Transporter substrate	Transporter effects	Comments
Non-nucleoside polymerase inhibitors					
ABT333	CYP2C8, CYP3A4 and CYP2D6 contribute approximately 60%, 30%, and 10% to ABT-333 metabolism, respectively[117]	ND	ND	ND	NA
BI 207127	ND	ND	P-gp, BCRP, OATP1B1, OATP1B3[42]	ND	NA

Abbreviations: AKR, aldoketoreductase; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DAA, direct-acting antiviral agent; MRP, multidrug resistance protein; NA, not applicable; ND, no data; OATP1, organic anion transporting polypeptide; P-gp, P-glycoprotein; UGT, uridine glucuronyl transferase.

Table 2

Direct-acting antiviral and antiretroviral scorecard

HIV therapy	HCV therapy					
	Boceprevir	**Telaprevir**	**Simeprevir**	**Faldaprevir**	**Daclatasvir**	**Sofosbuvir**
Atazanavir/ritonavir	×	✓	No data	No data	✓*	No data
Darunavir/ritonavir	×	×	×	✓	No data	✓
Fosamprenavir/ritonavir	No data	×	No data	No data	No data	No data
Lopinavir/ritonavir	×	×	No data	No data	No data	No data
Nelfinavir	No data	No data	No data	No data	No data	No data
Efavirenz	×	✓*	×	✓*	✓*	✓
Rilpivirine	✓	?	✓	No data	No data	✓
Etravirine	?	✓	No data	No data	No data	No data
Raltegravir	✓	✓	✓	No data	No data	✓
Elvitegravir/cobicistat	No data	No data	No data	No data	No data	No data
Maraviroc	✓*	✓*	No data	No data	No data	No data

× indicates the presence of an interaction, ✓ indicates the absence of a clinically important interaction, ✓* indicates that the combination is acceptable, but requires dose adjustment (see main text), ? indicates the presence of an interaction with uncertain clinical importance, ‘No data’ indicates no interaction data are currently available with the combination.