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Review Article

Drug-drug interactions between direct-acting antivirals and statins in the treatment of chronic hepatitis C

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Abstract

As the first line of treatment for hepatitis C virus (HCV) infection, direct-acting antivirals (DAAs) have greater efficacy and fewer adverse effects than other treatments; however, drug-drug interactions (DDIs) must be avoided when used in combination with other medications, such as statins. HCV patients are mostly in the need for polypharmacy, particularly the comedication of DAAs and cardiovascular drugs such as statins. This poses a risk of pharmacokinetic interactions between the two classes of drugs that may lead to severe myopathy or even rhabdomyolysis. Therefore, evaluating the severity of the DDIs and managing them is important. A multidisciplinary team-based model of care for HCV patients receiving DAAs can review the pharmacology profiles of other drugs for relevant DDIs with the DAAs, before prescription. Such a model can also follow the patients through the therapeutic cycle to make sure that their medical regimen is safe and effective. This article reviews the comedication rate and DDI-prevalence in HCV patients receiving statins along with the DAAs, details the mechanisms involved, gives recommendations for management, and shares our experience with a multidisciplinary team-based care program for the treatment of HCV patients.

Keywords: *Direct-acting antivirals, Drug-drug interactions, Multidisciplinary team-based care model, Statins*

Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, with approximately 71 million chronically infected individuals worldwide [1]. In Taiwan, HCV prevalence in the general population is 1.8%–5.5% [2]. The goal of HCV treatment is to cure the viral infection with a sustained virological response (SVR) and avoid the progression of disease to liver cirrhosis and hepatocellular carcinoma [1]. Interferon-free direct-acting antivirals (DAAs) are now the first HCV patients, providing superior efficacy, improved adverse effects, and a shortened treatment course in comparison with the previous standard of care [1,3,4]. The European Association for the Study of the Liver (EASL) guidelines recommend the use of DAAs – sofosbuvir/velpatasvir (Epclusa, Gilead Sciences, Inc., Foster City, CA, USA), glecaprevir/pibrentasvir (Maviret, AbbVie Inc., North Chicago, IL, USA), sofosbuvir/ledipasvir (Harvoni, Gilead Sciences, Inc., Foster City, CA, USA), and elbasvir/grazoprevir (Zepatier, Merck Sharp and Dohme, Kenilworth, NJ, USA) – for the treatment of HCV [1], all of which are marketed in Taiwan. Despite their efficacy, these regimens are associated with a few clinical challenges, such as in patients with decompensated cirrhosis, renal impairment [Table 1], and drug-drug interactions (DDIs).

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DAAs can be the substrates, inhibitors, or inducers of drug-metabolizing enzymes and drug transporters, which makes them both victims as well as perpetrators of DDIs [5-7]. Numerous studies have demonstrated that most patients with HCV infection have to undergo polypharmacy with a large number and diverse combination of medications, especially cardiovascular drugs such as the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors, commonly known as statins [8-14]. Statins are substrates of several drug transporters, such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP), and cytochrome p450 enzyme (CYP450) [15,16]. DAAs, except sofosbuvir, have pharmacokinetic interactions with various statins. Previous case reports have discussed the safety risk associated with excessive exposure to statins [17,18]; adverse effects of such exposure may include severe myopathy or rhabdomyolysis [17,18], which is potentially life-threatening.

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Table 1: Direct-acting antivirals recommended for hepatitis C virus infection in the European Association for the Study of the Liver guidelines and marketed in Taiwan

Brand name	Harvoni	Epclusa	Zepatier	Maviret
Drug	Sofosbuvir/ledipasvir	Sofosbuvir/velpatasvir	Elbasvir/grazoprevir	Glecaprevir/pibrentasvir
Genotype	1 2 4 5 6	1 2 3 4 5 6	1 4	1 2 3 4 5 6
Mechanism	NS5B inhibitor/NS5A inhibitor	NS5B Inhibitor/NS5A inhibitor	NS5A inhibitor/ protease inhibitor	NS5A inhibitor/protease inhibitor
Dosage	1# QD	1# QD	1# QD	3# QDCC
Dose adjustment with renal impairment	eGFR <30: Not recommended	eGFR <30: Not recommended	No adjustment necessary	No adjustment necessary
Dose adjustment with hepatic impairment	No adjustment necessary	No adjustment necessary	Child-Pugh B-C: C/I	Child-Pugh B: Not recommended Child-Pugh C: C/I
Posttransplant	O	O	X	X
Decompensate	O	O	X	X

EASL: European Association for the Study of the Liver, NS5B: Nonstructural protein 5B, NS5A: Nonstructural protein 5A, eGFR: Estimated glomerular filtration rate, C/I: Contraindication, O: Can use, X: Cannot use

This review aims to provide clinical guidance to medical caregivers on how to manage the potential DDIs between statins and DAAs in the treatment of HCV and hope to provide the information needed to make appropriate decisions in optimizing the DAA regimens for HCV treatment.

Interactions between direct-acting antiviral and 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins)

In this descriptive review, we discuss the DAA regimens – sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/ledipasvir, and elbasvir/grazoprevir – recommended in the EASL guidelines, all of which and marketed in Taiwan. The statins included are atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. All the drugs included in the review are listed in Table 2.

An extensive literature search was performed in July 2019. Search terms contained both generic and brand names of the drugs listed in Table 2. These drug names were combined with the search terms "DDI," "pharmacist," or "real-world" to identify peer-reviewed articles on PubMed between January 2010 and July 2019. All searches were performed in English. In addition, information from the summary of product characteristics (SmPC) approved by the European Medicine Agency and the prescribing information approved by the US Food and Drug Administration was also used. DDIs were checked with the University of Liverpool's HEP Drug Interactions Resource [19] and the Lexicomp database [20].

Before initiating DAA therapy, patients must be screened for chronic concomitant medication use, and DDIs can be checked by consulting with the University of Liverpool's HEP Drug Interactions Resource [19] or with the HCV clinical pharmacist. Statins are common concomitant medications in clinical practice for HCV treatment, with a prescription rate of approximately 4%–10% among HCV patients receiving DAA [Table 3] [14]. An observational prospective study in Spain, conducted on HCV patients above the age of 65 years, reported that 77.6% of the patients had at least one additional medication for a chronic condition. The most frequent chronic medications among these patients were anti-hypertensive drugs (58.3%), proton pump inhibitors (27.5%), benzodiazepines (22.5%), anti-diabetic agents (17.5%), and statins (10%). Before the initiation of HCV treatment, an adjustment of medication was needed for 35.8% of the patients, mainly for antihypertensive and statin therapies [14]. A nationwide cohort study from the Netherlands conducted on HCV patients (77% of which were on comedication) showed that anti-depressants (7.4%), proton pump inhibitors (7.1%), benzodiazepines (7.1%), and statins (only 4.12%) were the most frequently used pharmacotherapies by these patients in combination with the DAAs [21].

Statins are very commonly associated with DDIs, with rates ranging from 2.3% to 15.7% [13,14,21]. A retrospective cohort study conducted at a single Veterans Administration hospital in the USA found that the average rate of DDIs per patient was 1.85 (range 1–9). After acid suppression agents (20.4%), the next most common therapeutic class associated with DDIs was statins (15.7%) [13]. In a cohort study conducted in Germany, 261 HCV patients took a median of two drugs (range 0–15) at a time, and the rate of DDI events associated with simvastatin was 2.3% [22].

In a study conducted at our institution, clinical pharmacists reviewed HCV patients' medication profiles for relevant DDIs before the DAA therapy was initiated. The result showed a high rate of comedication in the patient population (mean comedication: 4.85/person), while the comedication rate with statins was 10%. The most common therapeutic classes associated with DDIs were antihypertensive drugs (31%), acid suppression agents (27%), and statins (17%).

Based on these reports and our real-world data [Table 3], statins are a common comedication therapeutic class closely associated with DDIs, especially in Taiwan. Therefore, choosing the correct DAA regimen and managing the DDIs are important aspects of HCV treatment for medical caregivers.

Drug-drug interactions between direct-acting antivirals and statins

In this review, potential DDIs were assessed and classified based on the information available at the University of Liverpool's HEP Drug Interactions Resource [19] and the Lexicomp database [20], and information about the

Table 2: Drug-drug interactions between statins and direct acting antivirals, including drug-metabolizing enzymes and drug transporters involved in the metabolism and distribution, results, and disease management

Direct acting antivirals	Harvoni (LED/SOF)						Epclusa (SOF/VEL)						Zepatier (EBR/GZR)						Maviret (GLP/PIB)					
	Substrate	P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4		P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4		P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4		P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4
	LED	S	S				VEL	S	S	S		S	EBR	S				S	GLP	S	S	S	S	S
		I	I					I	I	I	I			I	I					I	I	I	I	I
	SOF	S*	S*				SOF	S*	S*				GZR	S		S	S	S	PIB	S	S			S
															I			I		I	I	I	I	I

Atorvastatin		Atorvastatin concentration increase	Atorvastatin concentration increase	Atorvastatin concentration increase	Atorvastatin concentration increase
Substrate	**Inhibitor**				
$CYP3A4^{+++}$	$CYP3A4^{+}$	Tx:	Tx:	Tx:	Tx:
P-gp		Atorvastatin dose↓	Atorvastatin dose↓	Atorvastatin <20 mg/day	Contraindication
OATP1B1		Monitoring myopathy	Monitoring myopathy		
BCRP					
Fluvastatin		**Fluvastatin concentration increase**	**Fluvastatin concentration increase**	**Fluvastatin concentration increase**	**Fluvastatin concentration increase**
Substrate	**Inhibitor**				
CYP2C9	$CYP2C9^{++}$	Tx:	Tx:	Tx:	Tx:
CYP2D6	$CYP2C8^{+}$	Fluvastatin dose ↓	Monitoring myopathy	Fluvastatin <20 mg/day	Monitoring myopathy
CYP3A4				Monitoring myopathy	
CYP2C8					
OATP1B1					
BCRP					
Lovastatin		**Lovastatin concentration increase**	**Lovastatin concentration increase**	**Lovastatin concentration increase**	**Lovastatin concentration increase**
Substrate	**Inhibitor**				
$CYP3A4^{+++}$	$CYP2C9^{+}$	Tx:	Tx:	Tx:	Tx:
P-gp		Monitoring myopathy	Lovastatin dose↓	Lovastatin <20 mg/day	Contraindication
BCRP			Monitoring myopathy	Monitoring myopathy	
OATP1B1					
Pitavastatin		**Pitavastatin concentration increase**	**Pitavastatin concentration increase**		**Pitavastatin concentration increase**
Substrate	**Inhibitor**				
UGT1A3		Tx:	Tx:		Tx:
UGT2B7		Monitoring myopathy	Pitavastatin dose↓		Pitavastatin dose ↓
BCRP			Monitoring myopathy		
OATP1B1					

Contd..

Table 2: Contd...

Direct acting antivirals	Harvoni (LED/SOF)						Epclusa (SOF/VEL)						Zepatier (EBR/GZR)						Maviret (GLP/PIB)					
	Substrate	P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4		P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4		P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4		P-gp	BCRP	OATP1B1	OATP1B3	CYP3A4
	LED	S	S				VEL	S	S	S		S	EBR	S				S	GLP	S	S	S	S	S
		I	I					I	I	I	I			I	I					I	I	I	I	I
	SOF	S*	S*				SOF	S*	S*				GZR	S		S	S	S	PIB	S	S			S
															I			I		I	I	I	I	I

Pravastatin		Pravastatin concentration increase	Pravastatin concentration increase
Substrate	**Inhibitor**		
CYP3A4	CYP2C9^{+}	Tx:	Tx:
P-gp		Pravastatin dose↓	Pravastatin <20 mg/day or reduction by 50%
OATP1B1		Monitoring myopathy	
BCRP			

Rosuvastatin		Rosuvastatin concentration increase markedly	Rosuvastatin concentration increase	Rosuvastatin concentration increase	Rosuvastatin concentration increase
Substrate	**Substrate**				
CYP3A4	CYP3A4	Tx:	Tx:	Tx:	Tx:
CYP2C9	CYP2C9	Contraindication	Rosuvastatin <10 mg/day	Rosuvastatin <10 mg/day	Rosuvastatin <10 mg/day
OATP1B1	OATP1B1				
BCRP	BCRP				

Simvastatin		Simvastatin concentration increase	Simvastatin concentration increase	Simvastatin concentration increase	Simvastatin concentration increase markedly
Substrate	**Inhibitor**				
CYP3A4	CYP2C9^{+}	Tx:	Tx:	Tx:	Tx:
OATP1B1	CYP2C8^{+}	Simvastatin dose↓	Simvastatin dose↓	Simvastatin <20 mg/day	Contraindication
		Monitoring myopathy	Monitoring myopathy	Monitoring myopathy	

No Interaction Expected | Potential Interaction | Do Not Coadminister S*: Sofosbuvir is substrate of P-gp and BCRP; its metabolite GS-331007 is not a substrate of P-gp and BCRP.

↓: HMG-CoA reductase inhibitor dose reduction, +++: Major, ++: Moderate, +: Weak, BCRP: Breast cancer resistance protein; CYP: Cytochrome p450; OATP: Organic anion transporting polypeptide; P-gp: P-glycoprotein; UGT: Uridine glucuronyl transferase; LED: Ledipasvir; SOF: Sofosbuvir; VEL: Velpatasvir; EBR: Elbasvir; GZR: Grazoprevir; GLP: Glecaprevir; PIB: pibrentasvir; S: substrate; I: inhibitor

Table 3: Studies conducted on potential drug-drug interactions of concomitant medication of direct acting antivirals and statins

Reference	Study design	Number of patients	Drug	Comedication with statin (%)	DDI with statin (%)	Country	Major DAA regimen
J Clin Virol 2017;88:58-61[14]	Observational prospective study	120	Statin	10	NA	Spain	OBV/PTV/r + DSV±RBV (45%) LED/SOF±RBV (26.6%)
United European Gastroenterol J 2017;5:648-57[19]	Nationwide cohort	461	Statin	4.12	NA	Netherlands	NA
Ann Pharmacother. 2018;52:763-8[13]	Retrospective cohort study	300	Statin	NA	15.7	USA (Major: African American)	LED/SOF (56.3%) OBV/PTV/r + DSV±RBV (37.7%)
Clin Infect Dis 2016;62:561-7[21]	Cohort study	261	Simvastatin	NA	2.3	Germany	OBV/PTV/r+DSV (57.9%)
Aliment Pharmacol Ther 2018;48:1290-300[12]	Cross-sectional study	822	Statin	NA	NA	Taiwan	NA
Unpublished data	Cross-sectional study	461	Statin	10	17	Taiwan	LDV/SOF (24%) ELB/GZR (21%)

DDI: Drug-drug interaction, NA: Not available, DAA: Direct acting antiviral, LED: Ledipasvir, SOF: Sofosbuvir, OBV: Ombitasvir, PTV: Paritaprevir, r: Ritonavir, DSV: Dasabuvir, RBV: Ribavirin, ELB: Elbasvir, GZR: Grazoprevir

pharmacokinetics and metabolism of the DAAs and statins was obtained primarily from the package insert [16,23-27]. For most interactions, in the absence of clinical data, the information was based on the metabolic pathway of each drug used. Table 2 summarizes the DDIs between statins and DAAs – including information on the drug-metabolizing enzymes and drug transporters involved in the metabolism and distribution of the drugs – as well as the results and management of the DDIs.

Drug-drug interactions between ledipasvir/sofosbuvir and statins

Ledipasvir is a P-gp and BCRP substrate and inhibitor that can increase the intestinal absorption of the transporter substrates. Coadministration with strong P-gp inducers is contraindicated, while that with moderate P-gp inducers is not recommended, as this is believed to reduce the concentrations of ledipasvir and affect the agent's treatment efficacy. No clinically significant DDIs with ledipasvir and sofosbuvir mediated by CYP450 or Uridine Glucuronyl transferase (UGT) 1A1 are anticipated.

Sofosbuvir has a complex metabolism. A substrate of P-gp and BCRP, sofosbuvir is initially metabolized in the liver into a pharmacologically active nucleoside analog triphosphate–GS-461203. This is followed by dephosphorylation into GS-331007, the main circulating, inactive metabolite of sofosbuvir, used frequently to describe its pharmacokinetics [15]. GS-331007 is not a substrate of P-gp and BCRP [16], and it does not participate in DDIs with statins.

Statins are substrates, but not inhibitors or inducers of P-gp [26]; therefore, they would not affect the concentrations of ledipasvir/sofosbuvir. However, because ledipasvir is a BCRP inhibitor, the administration of ledipasvir/sofosbuvir together with rosuvastatin is contraindicated, due to the marked increase in the plasma concentrations of rosuvastatin upon coadministration. Dose adjustment or monitoring for myopathy is necessary when ledipasvir/sofosbuvir is used with other statins [Table 2].

Drug-drug interactions between sofosbuvir/velpatasvir and statins

Velpatasvir, a substrate of P-gp, BCRP, and OATP1B1 and an inhibitor of P-gp, BCRP, and OATP1B1/3, is metabolized by the enzymes–CYP2B6, CYP2C8, and CYP3A4. The prescribing information for velpatasvir states that its coadministration with statins may increase the statin concentration, and could be associated with an increased risk of myopathy, including that of rhabdomyolysis. Monitoring for these events is recommended. Sofosbuvir metabolism is discussed in Section 3.1.

Rosuvastatin may be administered with sofosbuvir/velpatasvir at a dose not exceeding 10 mg. In a drug-interaction study conducted with pravastatin and velpatasvir, no clinically significant interactions were observed between the two agents. Based on this observation, we assume that there are no DDIs between pravastatin and sofosbuvir/velpatasvir.

Dose adjustment or monitoring for myopathy is necessary when these agents are used with most statins, but not with pravastatin [Table 2].

Drug-drug interactions between elbasvir/grazoprevir and statins

Elbasvir and grazoprevir are mainly metabolized by CYP3A4 and are also substrates of P-gp. Thus, inducers of CYP3A can decrease the concentrations of elbasvir and grazoprevir, reducing the therapeutic effect; conversely, inhibitors of CYP3A can increase the concentrations of elbasvir and grazoprevir.

Atorvastatin is a substrate of CYP3A4, P-gp, and OATP1B1. Grazoprevir is a weak CYP3A4 inhibitor and could interfere with atorvastatin metabolism. Coadministration of elbasvir/grazoprevir (50/200 mg once daily) with atorvastatin (10 mg single dose) increases atorvastatin's area under the curve (AUC) by 94% and increases the maximum serum concentration (C_{max}) by 4.34 folds. The dose of atorvastatin should not exceed 20 mg/day when coadministered with elbasvir/grazoprevir.

Fluvastatin is a substrate of CYP2C8, 2D6, 2C9, 3A4, and OATP1B1; its lowest necessary dose, when coadministered with elbasvir/grazoprevir, should not exceed 20 mg/day. Coadministration of elbasvir/grazoprevir with lovastatin and simvastatin has not been studied, but the concentrations of these statins may be increased when used in combination with the DAA regimen. The doses of lovastatin as well as simvastatin should not exceed 20 mg/day when coadministered with elbasvir/grazoprevir.

Elbasvir and grazoprevir are also inhibitors of BCRP, a transporter that is at least partially responsible for rosuvastatin transport, although its role in the transport of other statins is unclear. Rosuvastatin's dose should not exceed 10 mg/day when coadministered with elbasvir/grazoprevir. Statins are not contraindicated to be used with elbasvir/grazoprevir, but dose-adjustments may be necessary for coadministration [Table 2].

Drug-drug interactions between glecaprevir/pibrentasvir and statins

Glecaprevir and pibrentasvir are P-gp substrates and are actively transported by BCRP. Glecaprevir is also a substrate for the hepatic transporter OATP1B1/3. Glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP, and OATP1B1/3 and have been shown to weakly inhibit CYP3A4 and UGT1A1 *in vivo*. This combination regimen shows strong DDIs and should not be administered with atorvastatin. In addition, glecaprevir and pibrentasvir should not be administered with lovastatin and simvastatin, because lovastatin inhibits P-gp, BCRP, and OATP1B1/3 and simvastatin inhibits OATP1B1.

Coadministration with fluvastatin and pitavastatin also requires caution, and close monitoring of myopathy is necessary. Statins should also be used at the lowest necessary dose when coadministered with glecaprevir/pibrentasvir. The European Summary of Product Characteristics (SPC) recommends that pravastatin's dose should not exceed 20 mg/day, while the United States Prescribing Information (USPI) recommends that pravastatin's dose should be reduced by 50% when prescribed in combination with glecaprevir/pibrentasvir.

Coadministration of glecaprevir/pibrentasvir and rosuvastatin (5 mg) increased rosuvastatin's C_{max} by 5.62 folds and AUC by 2.15 folds. The European SPC recommends that rosuvastatin's dose should not exceed 5 mg/day, whereas the USPI recommends that its dose should not exceed 10 mg/day when coadministered with glecaprevir/pibrentasvir.

Atorvastatin, lovastatin, and simvastatin should not be prescribed with glecaprevir/pibrentasvir. Treatment with alternative statins such as fluvastatin, pitavastatin, pravastatin, or rosuvastatin may be safer, but patients should be monitored for myopathy.

Summary

Because all statins are substrates of various drug transporters and/or drug-metabolizing enzymes that are inhibited by DAAs, combining DAAs and statins can result in a clinically relevant increase in statin plasma concentrations. Therefore, physicians should carefully monitor their patients for potential DDIs and signs of myopathy when combining statins with DAAs. Brief recommendations on the clinical management of the combination treatment have been summarized in Table 4.

Implementation of a multidisciplinary team-based model of care to manage hepatitis C virus patients on direct-acting antiviral therapy: Experience from the Dalin Tzu Chi Hospital

DDIs are a common clinical challenge in treatment with DAAs, as they can reduce the treatment efficacy and increase the safety risks associated with the DAA therapy. What is needed is a multidisciplinary team-based model of care in an HCV-DAA program. We started such a program at our institution in 2017, and included physicians, nurse practitioners, nurses, medical technologists, and pharmacists [Figure 1]. We shall share our protocol and experience here.

Step 1: Comprehensive medication has been summarized

Before DAA therapy, a physician evaluates the patient's information, including laboratory data and comorbidities, then proposes a DAA regimen and refers the patient to a clinical pharmacist. The information includes HCV viral load, HCV genotype, previous HCV-treatment experience, renal function test results, liver fibrosis score, Child-Pugh score, and hepatitis B virus (HBV) status. The patients sign a National Health Insurance pharma-cloud permission form, allowing a clinical pharmacist to screen for comedications taken within the past 3 months. Clinical pharmacists can help optimize patient care by recommending appropriate DAAs to providers through a careful review of DDIs, suggesting interventions to minimize adverse effects and monitoring subsequently for any DDIs [13,28]. Physicians then prescribe a suitable DAA regimen and adjust the medication over time, as needed, according to the pharmacist's suggestions.

Step 2: Patient education, counseling, and adherence evaluation

Before the first dose of a DAA, pharmacists provide medication counseling to patients, including educating them on the importance of adherence, checking for other comedications (including herbs and dietary supplements), and making sure patients are aware of the medication reconciliation

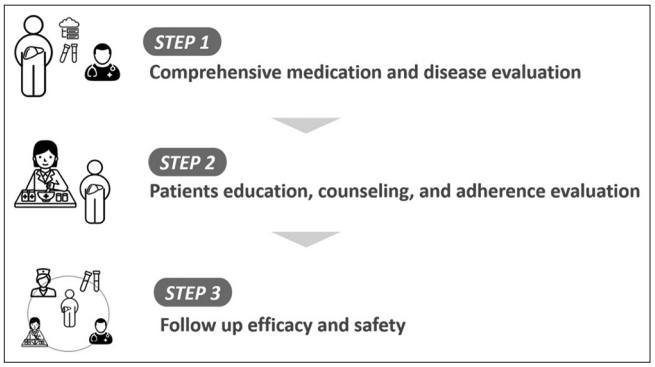
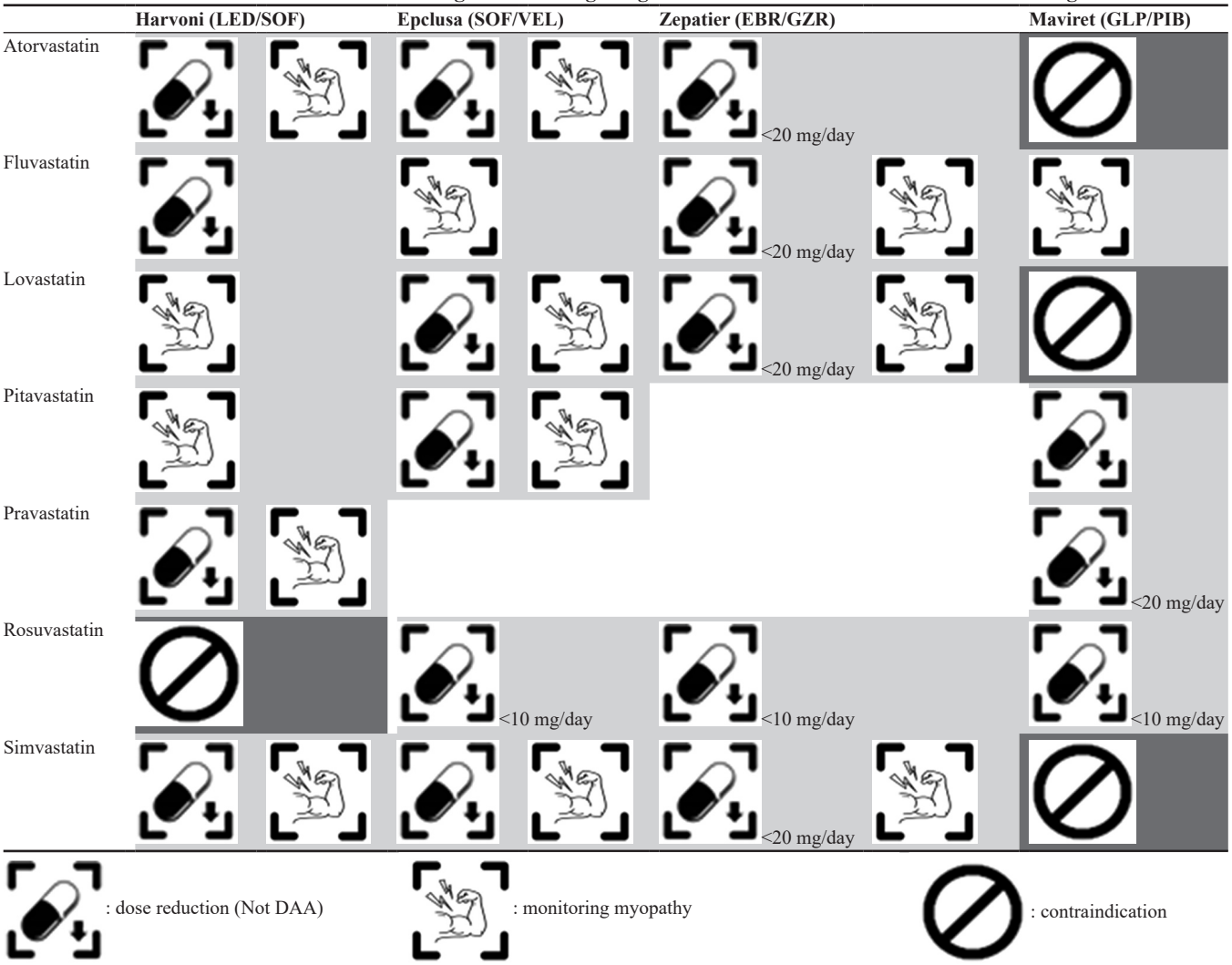


Figure 1: A multidisciplinary team-based model of care to manage hepatitis C virus patients on direct acting antiviral therapy

Table 4: Recommendations for the clinical management of drug-drug interactions between statins and direct-acting antivirals



DDIs: drug-drug interactions; DAAs: direct-acting antivirals; LED: ledipasvir; SOF: sofosbuvir; VEL: velpatasvir; EBR: elbasvir; GZR: grazoprevir; GLP: glecaprevir; PIB: pibrentasvir

by physicians. The provider encourages the patients to inform the pharmacist and other health-care providers of their current medication during the DAA therapy. MedTake test scores [29] are calculated before and after the medication counseling, to evaluate its effect. Nurses follow each patient's adherence by telephone and by interview during the outpatient visits. The team continues to follow the efficacy, safety, and DDIs associated with the DAAs over the course of therapy.

Step 3: Following up the efficacy and safety

The team measures the HCV RNA levels at week-4 to monitor the adherence and efficacy, and measures the SVR at week-12 to monitor the treatment success. Additional laboratory-test monitoring for safety may also be required, based on the regimen in use. For example, the liver biochemical tests of the patients should be monitored if they are on a protease-inhibitor containing regimen, renal function should be monitored if they are on a sofosbuvir-based regimen, and HBV DNA should be monitored in patients with evidence of the current or prior HBV infection.

Our experience

In 2018, 461 patients received a DAA regimen at the Dalin Tzu Chi Hospital. The average age of the patients was 65 years. In total, 85% of the patients had potential DDIs between the DAA and their comedication, 3% had contraindication, and 23% needed monitoring or dose adjustment. The pharmacist-recommendation-acceptance rate was 86%, higher in comparison with another study [13]. The acceptance rate of the recommendation of statins is 78%. In 22% of the cases, statins in use were withheld; in 8%, statin doses were reduced; in 3%, another statin was chosen; and in 17%, another DAA with relatively fewer DDIs was prescribed.

Conclusion

To avoid DDIs between statins and DAAs, special attention should be paid toward adjusting the dosage and monitoring the adverse effects. A multidisciplinary team-based model of care for the HCV patients being treated by DAAs could enhance the efficacy and safety of DAA therapy.

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Conflicts of interest

There is no conflict of interest.

References

1. European Association for the Study of the Liver Electronic address: Easloffice@easlofficeeu, European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018;69:461-511.
2. Bennett H, Waser N, Johnston K, Kao JH, Lim YS, Duan ZP, et al. A review of the burden of hepatitis C virus infection in China, Japan, South Korea and Taiwan. Hepatol Int 2015;9:378-90.
3. Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-99.
4. Omata M, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int 2016;10:702-26.
5. Burger D, Back D, Buggisch P, Buti M, Craxí A, Foster G, et al. Clinical management of drug-drug interactions in HCV therapy: Challenges and solutions. J Hepatol 2013;58:792-800.
6. Kiser JJ, Burton JR Jr., Everson GT. Drug-drug interactions during antiviral therapy for chronic hepatitis C. Nat Rev Gastroenterol Hepatol 2013;10:596-606.
7. El-Sherif O, Khoo S, Solas C. Key drug-drug interactions with direct-acting antiviral in HIV-HCV coinfection. Curr Opin HIV AIDS 2015;10:348-54.
8. Smolders EJ, Smit CT, de Kanter C, Dofferiiof AS, Arends JE, Brinkman K, et al. Brief Report: High Need to Switch cART or comedication with the initiation of DAAs in Elderly HIV/HCV-coinfected patients. J Acquir Immune Defic Syndr 2017;76:193-9.
9. Vermehren J, Peiffer KH, Welsch C, Grammatikos G, Welker MW, Weiler N, et al. The efficacy and safety of direct acting antiviral treatment and clinical significance of drug-drug interactions in elderly patients with chronic hepatitis C virus infection. Aliment Pharmacol Ther 2016;44:856-65.
10. Smolders EJ, Smit C, de Kanter C, Dofferhoff A, Arends JE, Brinkman K, et al. Management of drug interactions with direct-acting antivirals in Dutch HIV/hepatitis C virus-coinfected patients: Adequate but not perfect. HIV Med 2018;19:216-26.
11. Lauffenburger JC, Mayer CL, Hawke RL, Brouwer KL, Fried MW, Farley JF. Medication use and medical comorbidity in patients with chronic hepatitis C from a US commercial claims database: High utilization of drugs with interaction potential. Eur J Gastroenterol Hepatol 2014;26:1073-82.
12. Liu CH, Yu ML, Peng CY, Hsieh TY, Huang YH, Su WW, et al. Comorbidities, concomitant medications and potential drug-drug interactions with interferon-free direct-acting antiviral agents in hepatitis C patients in Taiwan. Aliment Pharmacol Ther 2018;48:1290-300.
13. Ottman AA, Townsend ML, Hashem MG, DiMondi VP, Britt RB. Incidence of Drug Interactions Identified by Clinical Pharmacists in Veterans Initiating Treatment for Chronic Hepatitis C Infection. Ann Pharmacother 2018;52:763-8.
14. Rodríguez-Osorio I, Cid P, Morano L, Castro Á, Suárez M, Delgado M, et al. Real life experience with direct-acting antivirals agents against hepatitis C infection in elderly patients. J Clin Virol 2017;88:58-61.
15. Smolders EJ, Jansen AM, Ter Horst PG, Rockstroh J, Back DJ, Burger DM. Viral hepatitis C therapy: Pharmacokinetic and pharmacodynamic considerations: A 2019 update. Clin Pharmacokinet 2019;58:1237-63.
16. Smolders EJ, Ter Horst PJ, Wolters S, Burger DM. Cardiovascular Risk Management and Hepatitis C: Combining Drugs. Clin Pharmacokinet 2019;58:565-92.
17. Lee JE, van Heeswijk R, Alves K, Smith F, Garg V. Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin. Antimicrob Agents Chemother 2011;55:4569-74.
18. Kanter CT, Luin MV, Solas C, Burger DM, Vrolijk JM. Rhabdomyolysis in a hepatitis C virus infected patient treated with telaprevir and simvastatin. Ann Hepatol 2014;13:452-5.
19. Liverpool Uo. University of Liverpool Hepatitis drug Interactions Website. Available from: https://www.hep-druginteractions.org/. [Last accessed on 2019 July 25].
20. Lexi-Comp. Drug-drug Interaction. Riverwoods, IL: Lexicomp, Wolters Kluwer Health, Inc.; 2019.
21. Smolders EJ, Berden FA, de Kanter CT, Kievit W, Drenth JP, Burger DM. The majority of hepatitis C patients treated with direct acting antivirals are at risk for relevant drug-drug interactions. United European Gastroenterol J 2017;5:648-57.
22. Höner Zu Siederdissen C, Maasoumy B, Marra F, Deterding K, Port K, Manns MP, et al. Drug-drug interactions with novel all oral interferon-free antiviral agents in a large real-world cohort. Clin Infect Dis 2016;62:561-7.
23. Harvoni. Available from: https://www.fda.gov.tw/MLMS/H0001D.aspx?Type=Lic&LicId=52026675. [Last accessed on 2019 July 25].
24. Zepatier. Available from: https://www.fda.gov.tw/MLMS/H0001D.aspx?Type=Lic&LicId=52026972. [Last accessed on 2019 July 25].
25. Epclusa. Available from: https://www.fda.gov.tw/MLMS/H0001D.aspx?Type=Lic&LicId=52027547. [Last accessed on 2019 July 25].
26. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions: An update. Expert Opin Drug Saf 2018;17:25-37.
27. Kellick KA, Bottorff M, Toth PP, The National Lipid Association's Safety Task Force. A clinician's guide to statin drug-drug interactions. J Clin Lipidol 2014;8:S30-46.
28. Mohammad RA, Bulloch MN, Chan J, Deming P, Love B, Smith L, et al. Provision of clinical pharmacist services for individuals with chronic hepatitis C viral infection: Joint Opinion of the GI/Liver/Nutrition and Infectious Diseases Practice and Research Networks of the American College of Clinical Pharmacy. Pharmacotherapy 2014;34:1341-54.
29. Raehl CL, Bond CA, Woods T, Patry RA, Sleeper RB. Individualized drug use assessment in the elderly. Pharmacotherapy 2002;22:1239-48.