DRUG INTERACTIONS

Clinical impact of pharmacokinetic interactions between the HCV protease inhibitor simeprevir and frequently used concomitant medications

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AIMS

Direct-acting antiviral agents (DAAs) for the treatment of hepatitis C (HCV) can be associated with drug–drug interactions (DDIs) with concomitant medications. The practical clinical implications of such DDIs are poorly understood. We assessed the clinical impact of possible pharmacokinetic (PK) interactions between simeprevir and frequently prescribed concomitant medications.

METHODS

This *post hoc* analysis pooled data from nine studies which evaluated simeprevir (SMV)-based interferon-free HCV treatment. Three classes of frequently used concomitant medications of interest (CMOIs) were analysed [antihypertensive drugs (AHDs), anxiolytic drugs (AXDs) and lipid-lowering drugs (LLDs)] and categorized as amber or green according to their DDI potential with SMV (green: no DDIs; amber: potential/known PK interactions). Concomitant medications not recommended to be coadministered with SMV were not included. The composite primary endpoint was defined as the frequency of either discontinuation, interruption or dose modification of the CMOI during 12 weeks of SMV treatment.

RESULTS

Few patients met the composite endpoint in the various subgroups. Patients on amber CMOIs tended to experience CMOI modification more often (13.4–19.4%) than those on green CMOIs (3.1–10.8%). There was no difference in the frequency of adverse events between patients taking green and those taking amber CMOIs.

CONCLUSIONS

In this large pooled analysis, coadministration of the evaluated commonly prescribed medications with known or potential PK interactions with SMV was manageable and resulted in few adjustments of concomitant medications. Our method could serve as a blueprint for the evaluation of the impact of DDIs.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- Direct-acting antiviral agents for the treatment of hepatitis C (HCV) can be associated with drug–drug interactions (DDIs) with concomitant medications.
- The practical implications of such DDIs in patients is poorly understood.
- We assessed the clinical impact of possible pharmacokinetic (PK) interactions between simeprevir and frequently prescribed concomitant medications.

WHAT THIS STUDY ADDS
- The impact on patient safety and on physicians' clinical management of coadministration of a HCV protease inhibitor and commonly prescribed comedication with PK interactions is described in detail for the first time.
- Our method could serve as a blueprint for evaluating of the impact of DDIs.

Introduction

With the introduction of interferon-free hepatitis C (HCV) therapy consisting of two or more direct-acting antiviral agents (DAAs), the treatment of HCV infection has become less complex, more tolerable and more effective compared with prior interferon-based therapy. However, all DAAs may potentially be associated with drug–drug interactions (DDIs) with concomitant medications due to shared transporter proteins or metabolic enzymes. The widespread deployment of DAAs makes optimal management of these DDIs a priority for successful therapeutic outcomes, as many of these concomitant treatments cannot be avoided [1].

HCV protease inhibitors (PIs) are metabolized via the **cytochrome P450** (CYP) system; therefore, a broad range of interactions involving enzyme inhibition and/or induction can be expected, but may vary between PIs [2].

Simeprevir (SMV) is a PI with established clinical efficacy in HCV genotypes 1 and 4, and antiviral activity against HCV genotypes 2, 5, and 6 [3]. Hepatic uptake of SMV is mediated by the organic anion-transporting polypeptide (OATP) 1B1/3 [4]. SMV is primarily metabolized by **CYP3A4**. Drugs that moderately or strongly inhibit or induce CYP3A4, or inhibit the hepatic transporter OATP1B1/3, may influence SMV plasma concentrations. On the other hand, SMV inhibits OATP1B1/3, P-glycoprotein 1 (P-gp), intestinal CYP3A4 and **breast cancer resistance protein** (BCRP) transporter. Coadministration of SMV with drugs that are substrates for any of these molecules may result in increased plasma concentrations of these drugs [4, 5].

Consequently, coadministration of SMV with drugs that moderately or strongly inhibit or induce CYP3A4 is not recommended [4]. Other medications have known or potential pharmacokinetic (PK) interactions with SMV but can still be coprescribed with caution or may need dose modification (e.g. calcium channel blockers and most statins).

HCV infection is associated with an increased risk of extrahepatic disease, including cardiovascular and renal disease, insulin resistance, diabetes mellitus type 2 and neuropsychiatric disorders [6–9]. Therefore, HCV patients often suffer from a higher total burden of disease, with an increased need for pharmacotherapy compared with HCV-uninfected individuals of a similar age. Polypharmacy has been found to be associated with an increased risk of adverse events (AEs) due to DDIs [10].

Previous research has focused mainly on the descriptive analyses of the prevalence of concomitant medications with the potential for interactions with DAAs, highlighting the risk of DDIs in subjects receiving a high number of contraindicated medications and the need for evaluation of potential DDIs to prevent AEs or the unnecessary risk of treatment failure [11, 12]. A recent analysis of over 400 HIV/HCV coinfected patients receiving DAAs together with their HIV treatment indicated that physicians are aware of potential DDIs between comedication and DAAs, in particular potential DDIs with antiretroviral therapy [13]. To date, the impact on patients and clinical management needs of potential PK interactions between DAAs and concomitant medication has not been assessed systematically. Understanding these practical implications may increase the level of confidence of healthcare providers in handling such DDIs and thus further improve HCV treatment outcomes.

The primary objective of the present analysis was to investigate the clinical management and treatment outcomes of coadministration of SMV with frequently prescribed concomitant medications of interest (CMOIs) with known or potential PK interactions with SMV.

Methods

Study design

In a *post hoc* analysis we pooled data from eight prospective interventional studies and one observational study of SMV-based interferon-free HCV therapy.

Studies selected for this analysis were Janssen-sponsored clinical trials evaluating interferon-free combinations of SMV in combination with **sofosbuvir** (SOF) and/or **daclatasvir** (DCV) with or without **ribavirin** (RBV) (Table 1) [14–22]. All studies were conducted in accordance with the 1975 Declaration of Helsinki, approved by independent ethics committees and registered with www.clinicaltrials.gov. Written informed consent was obtained from all patients prior to study initiation. The observational study was conducted at 33 US sites selected to reflect a diverse care setting; monitoring and source data verification were performed.

For the current analysis, the observation period was defined as the screening period (except for the observational study, which did not have a screening period) and the initial 12 weeks of SMV-based HCV treatment.

Three classes of CMOIs were selected for the analysis, owing to their broad use in this population and the potential for

Table 1

Studies included in this post-hoc analysis

Study identifier at ClinicalTrials.gov (Study name)	Type of study	Number of patients included in the analysis, n (%) N = 876 (100%)	Patient population	Reference No.
NCT02103699 (SONET)	Prospective observational	308 (35.2%)	Naïve or experienced, treated with SMV at various practice settings	19
NCT02114177 (OPTIMIST-1)	Interventional	155 (17.7%)	Naïve, no cirrhosis, treated with SMV + SOF	14
NCT02268864 (COMMIT)	Interventional	106 (12.1%)	Naïve, treated with SMV + DCV in GT 1b	18
NCT02114151 (OPTIMIST-2)	Interventional	103 (11.8%)	DAA-naïve, with cirrhosis, treated with SMV + SOF	15
NCT02165189 (GALAXY)	Interventional	46 (5.3%)	Liver transplant, treated with SMV + SOF ± RBV	20
NCT02278419 (OSIRIS)	Interventional	43 (4.9%)	Naïve or experienced Egyptians, GT 4, treated with SMV + SOF	16
NCT02262728 (IMPACT)	Interventional	40 (4.6%)	Cirrhosis, decompensated liver disease, GT 1 and 4, treated with SMV + SOF + DCV	22
NCT02250807 (PLUTO)	Interventional	40 (4.6%)	Naïve or experienced, GT 4, treated with SMV + SOF	17
NCT01938625 (SATURN)	Interventional	35 (4.0%)	Liver transplant, GT 1b, treated with SMV + DCV + RBV	21

DAA, direct-acting antiviral agents; DCV, daclatasvir; GT, HCV genotype; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir

DDIs: antihypertensive drugs (AHDs), anxiolytic drugs (AXDs) and lipid-lowering drugs (LLDs). Some of these drugs have known or potential DDIs with SMV, either as victims (SMV affects the concentration of other drugs, particularly with a narrow therapeutic window – *e.g.* calcium channel blockers, statins, anxiolytics) or as perpetrators (SMV concentration is affected by the other drug – e.g. some calcium channel blockers) [4, 5].

Treatment outcomes in patients taking drugs from more than one CMOI class were analysed in each class.

The CMOIs with known or potential DDIs with SMV were labelled 'amber', and CMOIs with no known or potential DDIs with SMV were labelled 'green'. The grouping into green and amber CMOIs was carried out according to the prescribing information for SMV [4] and the Liverpool DDI database (www.hep-druginteractions.org); in the absence of information from either source, expert advice was sought. Medications that are not recommended to be coadministered ('red') were disallowed in all clinical studies with SMV at study entry, and thus this category was not considered in the present analysis.

Study population

The overall population was defined as all study patients who had received SMV in combination with other DAAs (±RBV) and were observed for at least 12 weeks. To be included in the DDI analysis, patients also had to be receiving at least one drug from a class of CMOI; patients were required to have started this CMOI before study start or screening, and/or

during the screening period. Patients who had not been on a CMOI during screening or at study start but had started a CMOI after initiation of SMV therapy were excluded from the analysis. Two analysis sets were defined: the outcomes cohort, which included data from the screening period and the initial 12 weeks of SMV treatment, and patients receiving both green and amber CMOIs were evaluated twice, separately in each group; and the safety cohort, which included only patient data from the initial 12 weeks of SMV treatment. For both cohorts, patients taking CMOIs from several classes were counted in each CMOI class separately. In the safety cohort, patients had to be still on the CMOI at the start of SMV therapy, resulting in a slightly lower number of subjects. Additionally, in this cohort patients receiving both green and amber CMOIs were only counted in the amber group based on the assumption that safety outcomes would be driven mainly by amber drugs.

Outcome measures

The composite primary endpoint described dosing changes of the CMOI as an indicator for DDI management and was defined as either discontinuation (permanent discontinuation or interruption for ≥14 days), interruption (interruption of medication for 2–13 days) or dose modification (any increase or decrease from first recorded total daily dose or subsequent change, including interruptions up to 1 day of SMV treatment). Clinical information on the reasons for discontinuation, interruption or dose modification were not captured in the database, and thus not analysed

retrospectively. No direct analyses of DDIs on a PK level were performed. The primary endpoint was analysed in the outcomes cohort.

Secondary endpoints included the occurrence of AEs and AEs of interest (AEOIs), and discontinuation of SMV, regardless of causality. Adverse events of interest were defined as AEs that are either associated with the treated comorbidity, are signature AEs for the CMOI and would indicate either underdosing or overdosing. Secondary endpoints were analysed in the safety cohort.

Statistical analyses

Statistical comparisons of baseline demographics and disease parameters in green and amber groups were carried out in the safety cohort. Continuous parameters were tested using the Wilcoxon–Mann–Whitney test, and categorical parameters were tested using the chi-square test. Statistical analysis was conducted using the SAS statistical analysis software (SAS Institute Inc., Cary, N.C., USA). Representation of patients in both the green and amber groups precluded statistical comparison in the outcomes cohort.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [23], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [24, 25].

Results

Baseline characteristics

In total, 876 patients receiving SMV from the nine studies listed in Table 1 comprised the overall population, of which 47% (409/876) of the patients received AHDs, 17% (153/876) received AXDs and 11% (96/876) received LLDs. The observational study (SONET) contributed 35% (308/876) of the overall population, and 40% (162/409) of the patients receiving AHDs, 44% (67/153) of those receiving AXDs, and 50% (48/96) of those receiving LLDs. Table S1 presents the proportions of patients analysed from the different studies.

Demographics and disease parameters. Patients from the outcomes cohort represented a diverse population, with 31–41% women and 9–34% black/African American in any green or amber CMOI group. Information on the cirrhosis status was available for a large majority (91–100%), with cirrhosis prevalence ranging from 34% to 51% (Table S2). Some numerical (outcomes cohort) and statistically significant (safety cohort, Table S3) differences in demographic and disease parameters were detected between the green and amber groups.

Frequency of CMOIs. The prevalence of green *vs.* amber drugs differed by class of CMOI (Figure 1, Table 2). In the outcomes cohort, the majority of patients on AHDs received only green

AHDs (252/409, 61%), while the opposite was seen in patients on AXDs and LLDs (amber AXDs: 121/153, 79%; amber LLDs: 54/96, 56%) (Figure 1A–C). Patients receiving both green and amber CMOIs of the same drug class were most common in the AHD group (AHDs: 105/409, 26%; LLDs: 13/96, 14%; AXDs: 6/153, 4%). Table S3 lists the CMOIs administered.

The frequency of polypharmacy was high in the study population. In the outcomes cohort, most patients [67% on AHDs (272/409), 64% on AXDs (98/153), and 83% on LLDs (80/96)] were taking five or more of any type of concomitant medications. A relevant proportion of patients were taking more than one CMOI (Figure 2A–C).

In the safety cohort, more patients in the amber groups were receiving >1 CMOI (AHD, AXD, LLD) than patients in the green groups [AHDs: 69% *vs.* 36% ($P \leq 0.001$); AXDs: 18.7% *vs.* 4% ($P = 0.061$); LLDs: 20% *vs.* 11% ($P = 0.29$)].

## DDI management (composite primary endpoint in the outcomes cohort)

Most patients remained on their original CMOI without any modification during SMV treatment. Between 3.1% (green AXD) to 19.4% (amber LLD) of patients met the composite endpoint (Figure 3A–D).

Outcomes in patients on AHDs. Among patients on AHDs, the overall rate of CMOI treatment changes was similar for green and amber drugs [10.6% (38/357) in the green group, 14.0% (22/157) in the amber group; Figure 3A]. Most CMOI changes were either discontinuations or dose changes, with similar rates for amber and green drugs (Figure 3B). Most dose modifications of amber drugs were single dose changes (6/10, 60%, with four dose increases), with a subsequent discontinuation in a single patient. Half of all discontinuations of amber AHDs occurred during the screening period or on day 1 of SMV therapy (7/14).

Outcomes in patients on AXDs. Among patients on AXDs, the overall rate of CMOI treatment changes was lower in the green group [3.1% (1/32)] than in the amber group [13.4% (17/127)] (Figure 3A). A single patient stopped a green AXD, while 14/127 patients (11%) discontinued their amber AXD concomitant medication (Figure 3C), 5/14 (36%) during screening or on day 1 of SMV therapy. There was no clear pattern in patients stopping amber AXDs regarding their cirrhosis status, age, type of AXD or timing of discontinuation in relation to SMV treatment.

Outcomes in patients on LLDs. More patients (19.4%, 13/67) receiving LLDs classified as amber changed their CMOI treatment compared with 3/42 (7.1%) patients on green LLDs (Figure 3A,D). This difference was driven by statin dose reductions at a single timepoint ($n = 7$), mostly before SMV treatment was initiated (5/7) and in accordance with the US product information and EU Summary of Product Characteristics (SmPC) [4]. Four of these seven patients received a DCV-containing HCV regimen. One patient discontinued the statin following a dose change.

No major differences in the incidence of DDI management endpoints between clinical studies and the
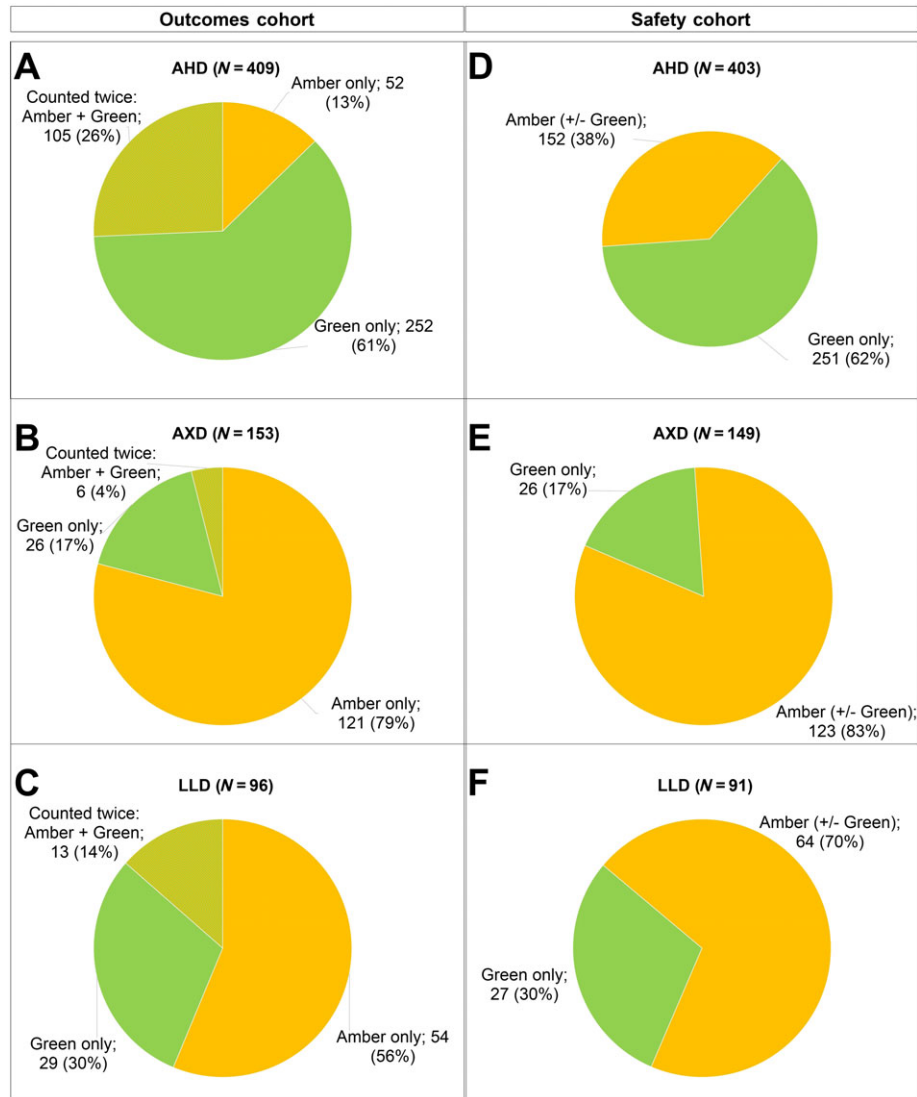
Figure 1

Proportion of green and amber CMOIs. Proportion of patients taking CMOIs classified as amber, green or both in the outcomes cohort and safety cohort. In both cohorts, most patients on AHDs were taking green AHDs only (A,D). The majority of patients on AXDs (B,E) and LLDs (C,F) were taking amber drugs only. There were slightly fewer patients in the safety cohort. AHD, antihypertensive drug; AXD, anxiolytic drug; CMOI, concomitant medication of interest; LLD: lipid-lowering drug

observational cohort during the treatment period were observed (data not shown). When treatment and screening periods were analysed separately, similar trends to the overall analysis were observed (data not shown). For patients on amber LLDs, CMOI changes were mainly carried out during the screening period, and mostly related to statins.

Safety and tolerability (safety cohort)

SMV in combination with green and amber CMOIs was well tolerated, with low rates of serious AEs (SAEs) and grade 3/4 events (Table 3). Similar rates were seen across all groups, except in patients taking green AXDs, where no such events occurred. Two patients discontinued SMV owing to AEs (grade 2–3 rash and sepsis) during the observation period. One patient on a green AHD discontinued SMV owing to death (road

traffic accident, not related to SMV). Another patient discontinued SMV after the observation period, but was included in the analysis as the AE started during the observation period.

AEs at least possibly related to SMV. AEs (all grades) at least possibly related to SMV were similar across CMOI groups, with no major differences between green and amber drugs (AHDs: green 37.1%, amber 44.1%; AXDs: green 34.6%, amber 39.8%; LLDs: green 40.7%, amber 32.8%; Table 3). Most of these related AEs were grade 1 or 2, with only seven patients experiencing grade 3 or 4 AEs. Serious AEs at least possibly related to SMV were reported in two patients: one patient on a green AHD (1/251, 0.4%) and one patient on an amber LLD (1/64, 1.6%).

Table 2

List of administered concomitant medication of interest (outcomes cohort)

AHDs started before study/screening and/or during screening			
Green (used in more than 3% of patients) (N = 357)		**Amber (all) (N = 157)**	
Lisinopril	99 (27.7%)	Amlodipine	102 (65.0%)
Furosemide	57 (16.0%)	Carvedilol	25 (15.9%)
Metoprolol	57 (16.0%)	Bisoprolol	20 (12.7%)
Hydrochlorothiazide	53 (14.8%)	Diltiazem	10 (6.4%)
Losartan	43 (12.0%)	Verapamil	4 (2.5%)
Spironolactone	39 (10.9%)	Felodipine	3 (1.9%)
Atenolol	26 (7.3%)	Indapamide	2 (1.3%)
Propranolol	26 (7.3%)		
Nadolol	25 (7.0%)		
Enalapril	20 (5.6%)		
Valsartan	17 (4.8%)		
Clonidine	11 (3.1%)		
AXDs started before study/screening and/or during screening			
Green (N = 32)		**Amber (N = 127)**	
Lorazepam	22 (68.8%)	Alprazolam	46 (36.2%)
Temazepam	6 (18.8%)	Zolpidem	43 (33.9%)
Oxazepam	3 (9.4%)	Clonazepam	26 (20.5%)
Bromazepam	1 (3.1%)	Diazepam	14 (11.0%)
Lormetazepam	1 (3.1%)	Buspirone	7 (5.5%)
		Clorazepate	2 (1.6%)
		Eszopiclone	2 (1.6%)
		Triazolam	2 (1.6%)
		Zaleplon	2 (1.6%)
		Zopiclone	2 (1.6%)
		Prazepam	1 (0.8%)
LLDs started before study/screening and/or during screening			
Green (N = 42)		**Amber (N = 67)**	
Omega 3 fish oil	31 (73.8%)	Simvastatin	22 (32.8%)
Ezetimibe	7 (16.7%)	Atorvastatin	19 (28.4%)
Fenofibrate	6 (14.3%)	Pravastatin	14 (20.9%)
Bezafibrate	1 (2.4%)	Lovastatin	5 (7.5%)
Fluvastatin	1 (2.4%)	Rosuvastatin	4 (6.0%)
		Gemfibrozil	3 (4.5%)

AHD, antihypertensive drug; AXD, anxiolytic drug; LLD, lipid-lowering drug

Safety of patients who discontinued their CMOI before or on day 1 of SMV initiation. Twelve patients (12/403, 3%) discontinued their AHD before or on day 1 of SMV treatment, six stopped an amber AHD (6/152, 4%) and six stopped a green AHD (6/251, 2%). Six patients started another AHD (two green, four amber) and two of them restarted their original AHD after 2 weeks to 5 months of discontinuation (one green, one amber). Eleven of these 12 patients experienced AEs, mostly of mild severity (grade 1–2). One grade 4 event (increased lipase) was reported, which resolved during SMV therapy and was considered not to be related to SMV.

Transient cardiovascular AEs of mild to moderate severity (grades 1–2) were reported in four of the 12 patients (two
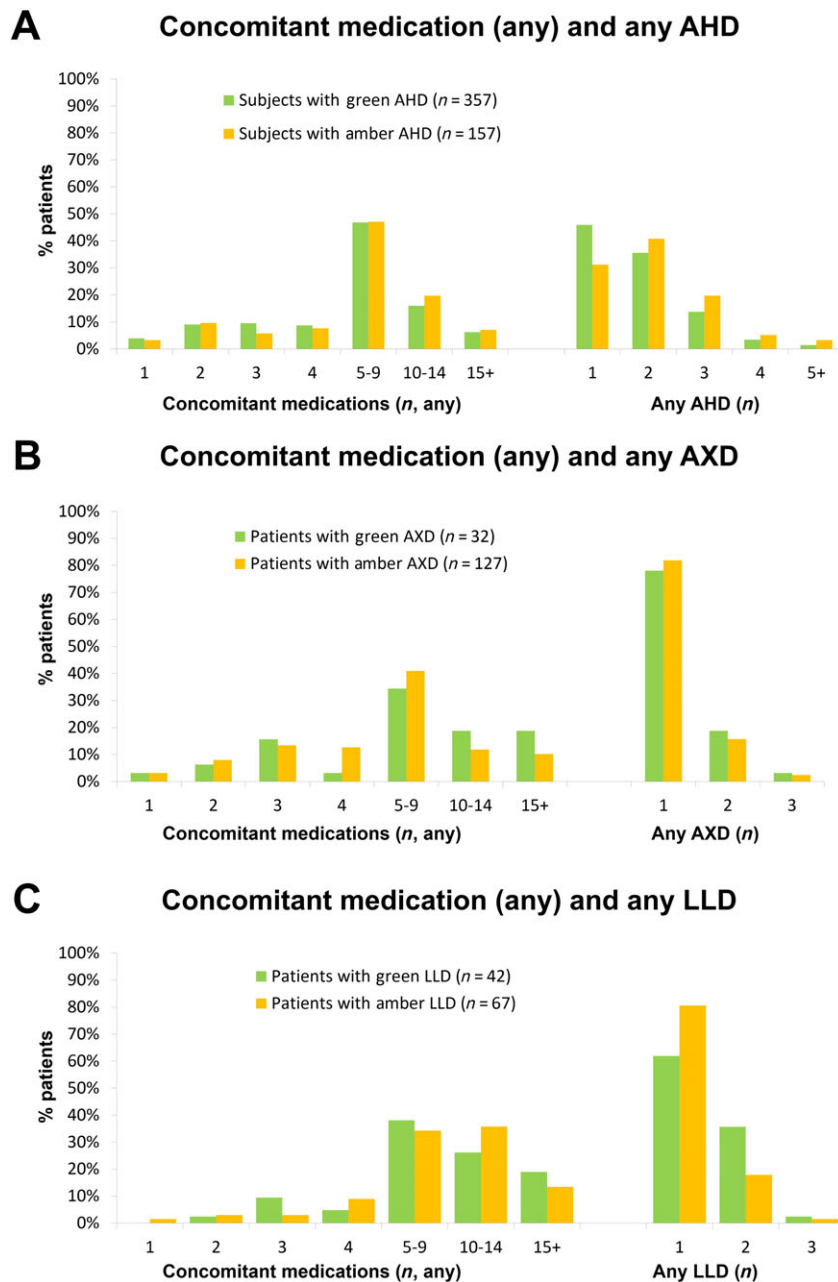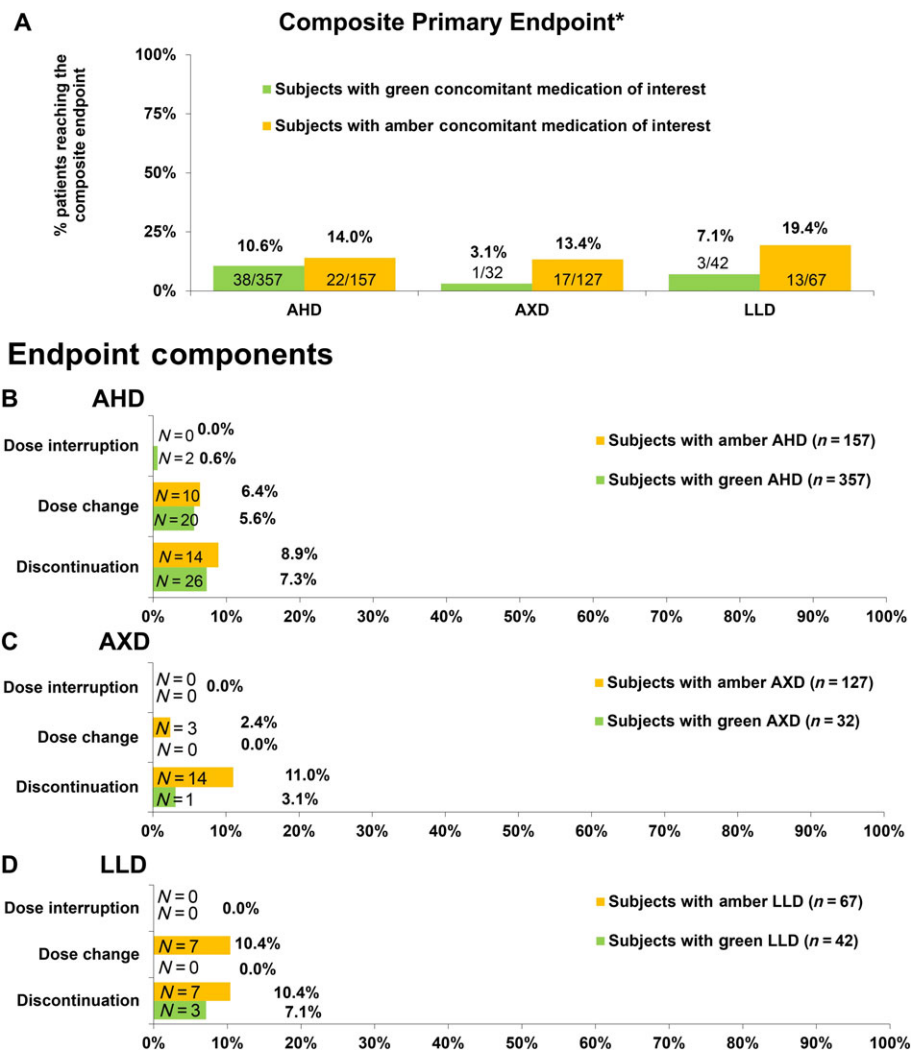
Figure 2
Frequency of CMOI (outcomes cohort). The number of concomitant drugs (any or additional CMOI) given in addition to SMV-based therapy are described. In all patient groups, rates of polypharmacy were similar for amber and green drugs. (A) Among patients on AHDs, the level of polypharmacy was high, with almost half of the patients taking any five to nine concomitant medications in addition to HCV therapy. It was common to take one or two AHDs. (B) Polypharmacy was high, with most patients on AXDs taking any five to nine concomitant medications. It was very common to take only one AXD, and less common to take two or three AXDs. (C) Among patients on LLDs, the frequency of any concomitant medications was higher compared with AHDs and AXDs, especially for patients taking 10 or more concomitant medications. It was very common to take only one LLD, and less common to take two or three LLDs. AHD, antihypertensive drug; AXD, anxiolytic drug; CMOI, concomitant medication of interest; HCV, hepatitis C virus; SMV, simeprevir; LLD, lipid-lowering drug

green AHDs, two amber AHDs) and not considered by the investigator to be related to SMV.

Among patients on AXDs, five patients discontinued their AXD before or on day 1 of SMV treatment (0 green AXDs, five amber AXDs). No patients switched to another AXD. One patient restarted the original AXD after 2 months of discontinuation. AEs during SMV treatment in these five patients were mostly mild (grades 1–2). No grade 3/4 AEs were reported. None of these five patients experienced AEs that indicated a withdrawal syndrome or experienced new or worsening psychiatric symptoms.

A

Composite Primary Endpoint*

■ Subjects with green concomitant medication of interest

■ Subjects with amber concomitant medication of interest

% patients reaching the composite endpoint

	AHD	AXD	LLD
green	10.6% (38/357)	3.1% (1/32)	7.1% (3/42)
amber	14.0% (22/157)	13.4% (17/127)	19.4% (13/67)

Endpoint components

B   AHD

■ Subjects with amber AHD (*n* = 157)
■ Subjects with green AHD (*n* = 357)

Dose interruption: *N* = 0 0.0% ; *N* = 2 0.6%
Dose change: *N* = 10 6.4% ; *N* = 20 5.6%
Discontinuation: *N* = 14 8.9% ; *N* = 26 7.3%

C   AXD

■ Subjects with amber AXD (*n* = 127)
■ Subjects with green AXD (*n* = 32)

Dose interruption: *N* = 0 ; *N* = 0 0.0%
Dose change: *N* = 3 2.4% ; *N* = 0 0.0%
Discontinuation: *N* = 14 11.0% ; *N* = 1 3.1%

D   LLD

■ Subjects with amber LLD (*n* = 67)
■ Subjects with green LLD (*n* = 42)

Dose interruption: *N* = 0 ; *N* = 0 0.0%
Dose change: *N* = 7 10.4% ; *N* = 0 0.0%
Discontinuation: *N* = 7 10.4% ; *N* = 3 7.1%

Figure 3

Primary outcome: treatment management of CMOI (outcomes cohort). Composite primary endpoint (A) and endpoint components (B, C, D). AHD, antihypertensive drug; AXD, anxiolytic drug; CMOI, concomitant medication of interest; LLD, lipid-lowering drug*Composite endpoint of either discontinuation, interruption or dose modification of the concomitant medication of interest

Five patients discontinued an LLD before or on day 1 of SMV treatment (two green LLDs, three amber LLDs). All amber LLDs were statins. None of the patients started another LLD or restarted the original LLD. AEs during SMV therapy (12 weeks) were mostly mild (grades 1–2); no grade 3/4 events were seen. One patient reported two SAEs (vomiting and abdominal pain), which resolved and were not considered to be related to SMV treatment. No AEs were linked to the withdrawal of LLDs, including two patients with ongoing hyperlipidaemia in their medical history.

AEOIs. Overall, AEIOs were rare. No differences among patients on green *vs.* amber CMOIs for AHDs and LLDs could be detected (Table S4). Among patients taking AXDs, patients on amber CMOIs showed higher frequencies of agitation (8.9% *vs.* 0.0%) and dizziness (4.1% *vs.* 0.0%) in comparison with patients on green CMOIs.

Discussion

We have presented a method to characterize the impact on patient safety and clinical management burden of the coadministration of DAAs with comedications with potential interactions. This is, to our knowledge, the first report of such an in-depth analysis in a diverse HCV-infected population with a high prevalence of advanced compensated liver disease and polypharmacy.

One of the strengths of the present analysis was the sizeable proportion of safety and outcomes data from carefully executed clinical trials, with strict capturing and follow-up of AEs and clinical outcomes. In addition, complete documentation of concomitant medication intake was available. As the clinical study protocols with SMV generally did not require changes in the dosage of the CMOIs analysed in the present study (e.g. for statins, only general guidance similar to the SmPC was included), the management of concomitant

Table 3

Safety summary and tolerability of simeprevir (SMV) in combination with green and amber concomitant medication of interest (safety cohort)

Drug class of interest (Patients on both green and amber drugs were counted only in the amber group)	AHD (N = 403)		AXD (N = 149)		LLD (N = 91)	
	Green n = 251 (62%)	Amber n = 152 (38%)	Green n = 26 (17%)	Amber n = 123 (83%)	Green n = 27 (30%)	Amber n = 64 (70%)
≥1 AE (all grades), n (%)	159 (63.3%)	98 (64.5%)	17 (65.4%)	79 (64.2%)	19 (70.4%)	35 (54.7%)
≥1 SAE, n (%)	18 (7.2%)	9 (5.9%)	0	9 (7.3%)	2 (7.4%)	2 (3.1%)
≥1 Grade 3/4 AE, n (%)	22 (8.8%)	11 (7.2%)	0	7 (5.7%)	2 (7.4%)	5 (7.8%)
Discontinuation of SMV (any AE), n (%)	3[a,b](1.2%)	1[c](0.7%)	0	0	1[b](3.7%)	0
AEs at least possibly related to SMV						
≥1 AE (all grades), n (%)	93 (37.1%)	67 (44.1%)	9 (34.6%)	49 (39.8%)	11 (40.7%)	21 (32.8%)
≥1 Grade 3/4 AE, n (%)	4 (1.6%)	2 (1.3%)	0	1 (0.8%)	0	0
≥1 SAE, n (%)	1[d](0.4%)	0	0	0	0	1[e](1.6%)

AE, adverse event; AHD, antihypertensive drug; AXD, anxiolytic drug; LLD, lipid-lowering drug; n, number of patients; SAE, serious adverse event
[a]Reasons for discontinuation: hyperbilirubinaemia Grade 4 (possibly related; recovered), sepsis (not related; recovered), road traffic accident (not related; death)
[b]Reason for discontinuation: sepsis (not related; recovered) – same patient as in green AHD group
[c]Reason for discontinuation: rash Grade 2/3 (probably related; recovered)
[d]Anaemia Grade 3 and hyperbilirubinaemia Grade 4 (possibly related to SMV therapy; recovered/resolved)
[e]Photosensitivity reaction Grade 1 (possibly related to SMV therapy; recovered/resolved)

medication in these studies resembles routine clinical practice. In addition, the observational study contributed a substantial proportion of the study population, reflecting common clinical practice. Investigators in the observational study were obliged to record changes in a participant's concomitant medications. Moreover, monitoring and source data verification took place in the observational study, and dose changes possibly related to DDI management were most likely reported. This was confirmed by an additional analysis separating the data from the clinical trials, and the observational study revealing similar low rates of DDI management incidence during the treatment period in both settings.

Most patients remained on their original CMOI without dose change or interruption during SMV treatment. In addition, only small differences in CMOI management between green and amber drugs were observed. As green CMOIs are not known to interact with SMV, this indicates that SMV treatment in the presence of amber CMOIs with known or potential PK interactions is manageable with few adaptations. If dose changes or discontinuations were considered necessary, they were to similar degrees implemented during screening and during SMV treatment, except for changes of amber LLDs. Most of these LLDs were statins, which may have been pre-emptively adjusted for potential DDIs with SMV. This further indicates that patients on some statins may – in accordance with the label – require DDI management prior to SMV treatment. In the studies analysed, healthcare professionals were aware of potential DDIs and the recommended coadministration, and followed clinical recommendations. However, as the number of patients in the various subgroups decreases, especially for AXDs and LLDs, interpretations should be made with caution.

In this group of well-managed patients, 12 weeks of SMV-based treatment were generally well tolerated, despite a high level of polypharmacy and a large proportion of patients with advanced disease, with most AEs being of mild or moderate severity.

No major differences in the safety outcomes were observed between green and amber CMOIs for AHDs and LLDs, despite some differences existing in baseline parameters among patients on AHDs, and patients on amber drugs tending to have a higher frequency of polypharmacy. Patients on amber AXDs had a higher rate of AEOIs, such as agitation; however, we could not determine whether these AEs were due to DDIs. Moreover, significant differences in baseline parameters existed between the green and amber groups.

In patients who discontinued their CMOIs before starting SMV therapy, few AEs were reported. These AEs were not likely to be associated with the discontinuation of the respective CMOI. For discontinuations of LLDs, the observation period may have been too short for the development of any AE linked to hyperlipidaemia.

Limitations

The present study was a *post hoc* analysis. Patients on green and amber AHDs and AXDs differed slightly in key disease and demographic parameters and in polypharmacy rates, limiting comparisons between groups. Outcomes were not differentiated for patients taking drugs from several drug classes of interest. In the database, there was no information available on whether dose changes or dose interruptions of CMOIs were due to DDIs with HCV treatment. In cases where DDIs may have been the reason for reaching the primary or

secondary endpoint, the data did not allow us to identify the interacting drugs (SMV, DCV, SOF or RBV).

We did not analyse the potential for DDIs in patients receiving multiple concomitant medications, as the main objective was to elucidate the impact of the short-term anti-HCV treatment. However, some of the CMOI changes could have been due to interactions with drugs other than the DAAs.

Clinicians may already have taken the ongoing concomitant medication into account prior to screening, potentially resulting in recruitment of patients with easy to manage concomitant medications. On the other hand, clinical trials document and grade safety events in a much more complete, consistent and reproducible manner compared with real-world cohorts, providing a robust picture of the real safety issues. Further, in the present analysis a high degree of polypharmacy was still seen, so we do not consider exclusion of certain comedications to be a relevant confounder of our analysis. In an unselected sample of 261 DAA-naive HCV-mono-infected patients, only 0.4% received a concomitant medication that was strictly contraindicated for SMV–SOF, while drugs with potential DDIs (category amber) were found in 31% of the sample [11]. Our dataset thus was a good reflection of the distribution of comedications used by mono-infected patients in routine clinical practice.

Conclusions

In the present *post hoc* analysis of pooled data from eight clinical trials and one observational study with interferon-free SMV combinations, coadministration of the evaluated medications with known or potential PK interactions with SMV was manageable. This observation is encouraging and should increase the level of confidence of healthcare providers in handling such DDIs, thereby improving the management of HCV patients. However, healthcare providers should remain vigilant of potential DDIs when administering HCV medication.

Our method could serve as a blueprint for the evaluation of the impact of DDIs in other areas – e.g. with other DAAs, to elucidate the clinical consequences of administering DAAs in a setting with a high rate of comorbidities and concomitant medication. With this method, it would be possible to utilize clinical study outcomes data in retrospect, in the absence of prospectively collected PK data.

Competing Interests

Contributors

F.M., C.H.S., S.K., D.B., M.C., R.K., M.B., W.J., M.S. and I.L.D. were responsible for the study concept and design. F.M., C.H.S., S.K., D.B., M.C., S.O.M., C.B., W.J. and M.S. carried out analysis and interpretation of the data. F.M., C.H.S., S.K., D.B., M.C., C.B. and M.S. drafted the manuscript, with editorial support from T.O.M. Life Science Consulting. All authors critically revised and approved the manuscript.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13519/suppinfo

Table S1 Patients taking green *vs*. amber concomitant medication of interest by trial (outcomes cohort)
Table S2 Key baseline demographic and disease parameters (outcomes cohort)
Table S3 Key baseline demographic and disease parameters (safety cohort)
Table S4 Frequency of adverse events of interest (safety cohort)