Poster 172

Risk of Multiple Drug Interactions Potentially Linked to Safety in Patients Receiving Pangenotypic Direct-acting Antivirals for the Treatment of Hepatitis C

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Introduction

- DAAs share pharmacokinetic (PK) pathways with many comedications commonly administered to patients with chronic HCV[1–3]
- APASL, EASL and AASLD guidelines recommend a thorough DDI risk assessment prior to starting DAA therapy and before starting comedications[4–6]
- Previous studies have evaluated DDIs by studying pairwise interactions in HCV patients receiving DAAs and another medication, however this does not reflect the polypharmaceutical reality of many HCV patients[7–11]

Objective

- The aim of this study is to describe the proportion of HCV patients with multiple DDIs and the impact these have on the safety and effectiveness of patients treated with SOF/VEL or GLE/PIB

Methods

- A retrospective, observational study from a Spanish database of 1.8 million people between 2017 and 2020
- Patients included in this analysis had chronic HCV infection and were treated with either GLE/PIB or SOF/VEL
- Patient demographics and the presence of comorbidities and comedications were evaluated at the index date

- DDIs were identified at index date using the HEP Drug Interactions database (University of Liverpool)12
- They were recorded by drug therapeutic group and classified according to:

Strength of interaction	Predicted clinical outcome	
Contraindicated	↑comedication	Possible impact on safety
Significant interaction	↓DAA	Possible impact on efficacy
Weak interaction	↑DAA	Possible impact on safety

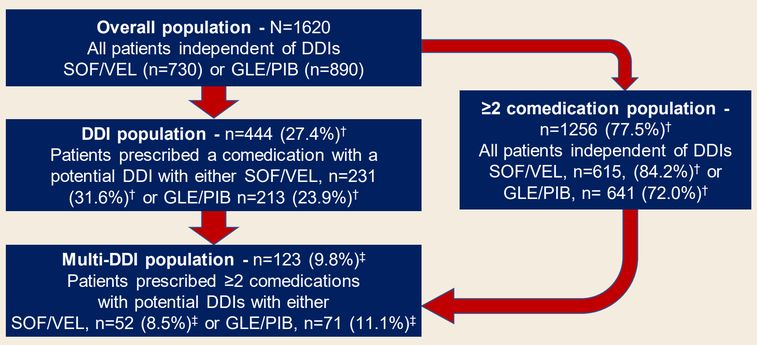
- Multi-DDIs were defined as ≥2 comedications, each with a DDI with their DAA treatment

- Adverse events (AEs) potentially connected to DDIs were identified by the ICD-9-CM, codes 990–995 and E930–E949 during DAA treatment period. The associated comedications for the AEs and the drug classification were recorded
- SVR data were not available, so effectiveness was assessed by recording the number of patients who required a new course of DAA therapy to be started within 6 months after finalising previous SOF/VEL or GLE/PIB treatment; a positive response was assumed for all other patients

Results

- 1620 patients were included, 730 with SOF/VEL and 890 with GLE/PIB (Figure 1)
- More than 3 out of 4 patients (77.5%) received ≥2 comedications
- Overall, 27.4% of patients were prescribed ≥1 comedication, each with a DDI with their DAA treatment
- From the population taking ≥2 comedications, the risk of multi-DDI with DAAs was 9.8%

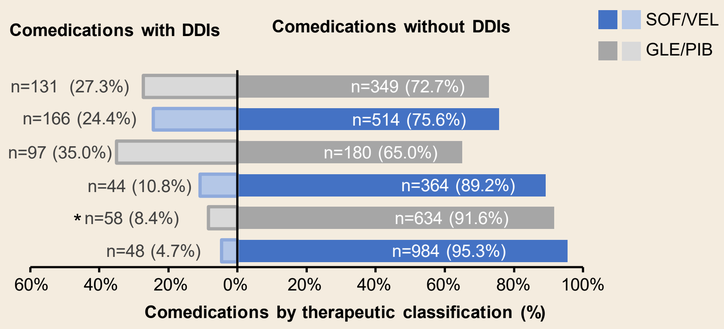
Figure 1: Patient population stratified by comedication use and risk of DDIs



†Percentage relative to overall population; ‡Percentage relative to ≥2 comedication population.

- The median age (55 vs 53 years, p<0.001) and fibrosis score F3/F4 (37.8% vs 28.0%, p<0.001) were higher for SOF/VEL-treated patients compared with GLE/PIB-treated patients
- In the overall population, patients were prescribed 3 comedications on average. The number of prescribed comedication was significantly higher for SOF/VEL-treated patients compared with GLE/PIB-treated patients (3.8 vs 2.3, p<0.001)

Figure 2: Percentage of prescribed comedications and potential DDIs by therapeutic classification in overall population

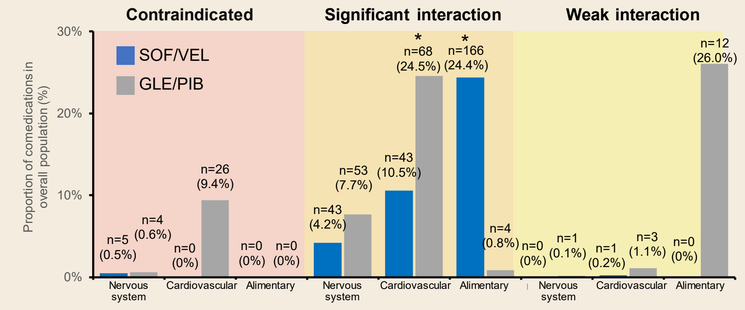


*p=0.002; **p<0.001

- Nervous system, cardiovascular and alimentary comedications were the most prescribed comedications in HCV patients accounting for 35.8%, 14.2% and 24.1%, respectively
- Patients prescribed comedications with potential DDIs were higher across the three most common comedication groups in GLE/PIB compared with SOF/VEL (Figure 2)
  - Nervous system comedications were 4.7% vs 8.4% (p=0.002), cardiovascular were 10.8% vs 35.0% (p<0.001) and alimentary were 24.4% vs 27.3% for SOF/VEL vs GLE/PIB, respectively

Results, cont'd

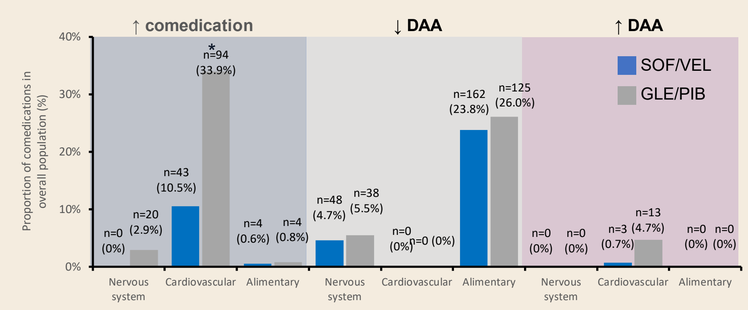
Figure 3: Strength of the DDIs accordingly to the most common comedications in the overall population



*p<0.05; n=total number of comedications with predicted DDI stratified by strength of interaction in the overall population

- Interactions with cardiovascular comedications were most likely to be contraindicated in the GLE/PIB treatment group (9.4%) (Figure 3)

Figure 4: Predicted clinical outcomes accordingly to the most common comedications in the overall population



*p<0.05; n=total number of comedications with predicted DDI stratified by clinical outcome in the overall population

- DDIs predicted to increase comedication concentration (with a possible impact on safety) were numerically higher in GLE/PIB-treated patients compared with SOF/VEL-treated patients across the three main therapeutic classifications (nervous system, cardiovascular and alimentary) (Figure 4)
  - Nervous system comedications were 0% vs 2.9%, in cardiovascular comedications, were 10.5% vs 33.9% (p<0.05) in alimentary comedications were 0.6% vs 0.8% for SOF/VEL- vs GLE/PIB-treated patients, respectively

Table 1: Summary table of adverse events by DAA and most common comedications in the overall population

Comedication group with AE [AEs by DAA treatment group]	SOF/VEL	GLE/PIB
Nervous system, n	**0**	**4**
Antipsychotics, n (%, n/N)†	*0 (0%; 0/90)*	*2 (12.5%; 2/16) [extrapyramidal, sedation]*
Fentanyl, n (%, n/N)†	*0 (0%; 0/9)*	*1 (33.3%; 1/3) [digestive]*
Oxcarbazepine, n (%, n/N)†	*0 (0%; 0/4)*	*1 (33.3%; 1/3) [digestive]*
Cardiovascular, n	**4**	**9**
Lipid-lowering drugs, n (%, n/N)†	*2 (5.0%; 2/40) [myalgia/myopathy]*	*6 (17.1%; 6/35) [myalgia/myopathy]***
Enalapril, n (%, n/N)†	*1 (1.9%; 1/52) [respiratory]*	*2 (6.1%; 2/33) [respiratory]**
Carvedilol, n (%, n/N)†	*1 (16.6%; 1/6) [bradycardia]*	*1 (12.5%; 1/8) [bradycardia]*
Alimentary, n	**0**	**1**
Omeprazole, n (%, n/N)	*0 (0%; 0/119)*	*1 (1.1%; 1/95) [digestive]*
Total, n (%, n/total)‡	**4 (0.5%; 4/730)**	**14 (1.6%; 14/890)***

*p<0.05; **p<0.001; AE: adverse event (see methods), n: number of patients with AEs, N: Number of patients receiving specific comedication linked to AEs; †Percent relative to patients treated with the comedication with AEs; ‡Percentage relative to the overall population (total).

- GLE/PIB-treated patients reported 3.5 times higher AEs compared with SOF/VEL-treated patients (14 vs 4; p<0.05) (Table 1)
- AEs were numerically higher in patients concomitantly prescribed with lipid-lowering drugs, 17.1% (6/35) vs 5.0% (2/40) [p<0.001] in patients treated with GLE/PIB vs SOF/VEL, respectively
- AEs in patients concomitantly prescribed with antipsychotics were recorded in 12.5% (2/16) vs 0% (0/90) patients treated with GLE/PIB vs SOF/VEL, respectively

Table 2: Multi-DDI population: Demographics and characteristics of multi-DDI population‡

Demographic characteristics	SOF/VEL (n=52)	GLE/PIB (n=71)	Total (n=123)
Median age, years (IQR)	59 (54–73)	61 (52–72)	60 (53–73)
Male, n (%)	30 (57.7)	38 (53.5)	68 (55.3)
Specific comorbidity			
FIB-4 score, (%)			
F0–F1, <1.45 points, n (%)	7 (13.5)	15 (21.1)	22 (17.9)
F2, 1.45–3.25 points, n (%)	14 (26.9)	20 (28.2)	34 (27.6)
F3–F4, >3.25 points, n (%)	31 (59.6)	36 (50.7)	67 (54.5)
Potential multi-DDI outcomes			
Patients prescribed ≥2 comedications with risk of increased comedication concentration, n (%)†	6 (11.5)	23 (32.4)*	29 (23.6)
Patients prescribed ≥2 comedications with risk of decreased DAA concentration, n (%)†	26 (50.0)	22 (31.0)**	48 (39.0)

*p=0.007, **p=0.033; †Multi-DDI, ≥2 comedications with DDIs with DAA treatment; ‡percentage relative to multi-DDI population

- Most patients with AEs had a multi-DDI profile (88.8%; 16/18). These patients were older (60 [53–73] years vs 54 [48–60] years) than the overall population and a higher proportion were F3/F4 (54.5% and 32.4%, respectively)
- Of the 123 multi-DDI patients, 13.0% had AEs: 18.3% (13/71) of GLE/PIB patients and 5.8% (3/52) of SOF/VEL patients (p<0.05)
- The risk of increasing comedication in patients with multi-DDIs was higher in the GLE/PIB treatment group than in the SOF/VEL treatment group (32.4% vs 11.5%; p=0.007) (Table 2)
- There was an association between AEs and DDIs predicted to increase comedication concentration in the multi-DDI population:
  - Almost 2/3 of patients 62.5% (10/16) with AEs were reported in patients prescribed ≥2 comedications predicted to increase comedication concentration
  - 33% (10/29) of patients prescribed ≥2 comedications predicted to increase comedication concentration reported AEs

- In GLE/PIB-treated patients with a multi-DDI profile, AEs were associated with nervous system, cardiovascular and alimentary comedications, while in SOF/VEL-treated patients with a multi-DDI profile, all AEs were associated with cardiovascular comedications (Table 3)
- From the multi-DDI population:
  - Patients prescribed cardiovascular medications with predicted DDIs reported associated AEs in 12.5% (3/24) and 18.6% (8/43) of SOF/VEL- and GLE/PIB-treated patients, respectively
    - Cardiovascular AEs were mainly associated with statins (7/11). Patients prescribed either atorvastatin or simvastatin reported associated AEs in 13.3% (2/15) and 35.7% (5/14) of SOF/VEL- and GLE/PIB-treated patients, respectively
  - Patients prescribed nervous system comedications reported associated AEs in 0% (0/24) and 13.8% (4/29) of SOF/VEL- and GLE/PIB-treated patients, respectively
  - Patients prescribed alimentary comedications reported associated AEs in 0% (0/49) and 1.7% (1/58) of SOF/VEL- and GLE/PIB-treated patients, respectively

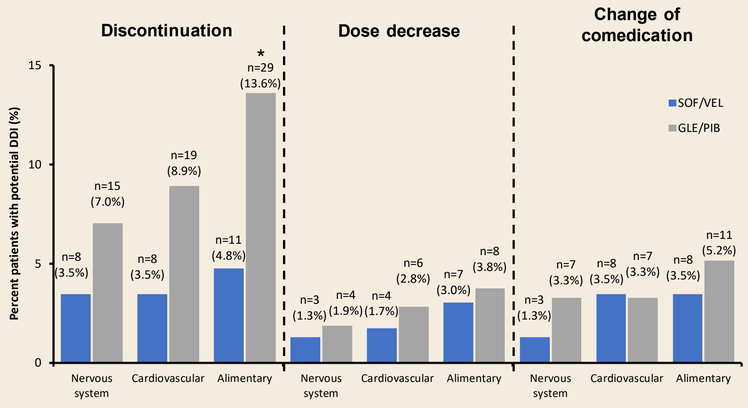
Table 3: Comedications (coloured by strength of DDI) used by SOV/VEL- and GLE/PIB-treated patients with a multi-DDI profile and reported AEs†

DAA	Comed group with associated AE	Adverse event (comedication associated)	Comedications by potential DDI outcome								No. of patients
			↑ comedication				↓ DAA		↑ DAA		
SOF/VEL	Cardio-vascular (n=24)	Myalgia/myopathy (atorvastatin)	Atorvastatin	Carvedilol			Omeprazole				1
		Myalgia/myopathy (simvastatin)	Simvastatin	Silodosin			Omeprazole				1
		Bradycardia (carvedilol)	Carvedilol				Metamizole	Omeprazole			1
GLE/PIB	Nervous system (n=29)	Digestive (oxcarbazepine)					Oxcarbazepine	Omeprazole			1
		Extrapyramidal (quetiapine)	Carvedilol‡	Quetiapine							1
		Sedation (paliperidone)	Paliperidone				Pantoprazole				1
		Digestive (fentanyl)	Fentanyl	Bilastine	Tacrolimus		Omeprazole	Sevelamer			1
	Cardio-vascular (n=43)	Myalgia/myopathy (atorvastatin)	Atorvastatin	Quetiapine			Omeprazole				1
		Myalgia/myopathy (simvastatin)	Simvastatin				Rabeprazole		Candesartan		1
		Myalgia/myopathy (atorvastatin)	Atorvastatin	Enalapri			Dulaglutide	Omeprazole			1
		Myalgia/myopathy (atorvastatin)	Atorvastatin	Carvedilol‡	Repaglinide	Tacrolimus	Ranitidine				1
		Myalgia/myopathy (simvastatin)	Simvastatin	Fentanyl	Quetiapine	Tacrolimus	Metamizole	Omeprazole			1
		Bradycardia (carvedilol)	Carvedilol‡	Amiodarone			Liraglutide				1
		Respiratory (enalapril)	Atorvastatin	Enalapril			Metamizole	Omeprazole			1
		Respiratory (enalapril)	Enalapril				Metamizole				1
	Alimen-tary (n=58)	Digestive (omeprazole)	Olmesartan				Metamizole	Omeprazole			1

n=total number of patients from the multi-DDI population prescribed at least one comedication with a potential DDI according to therapeutic classification
†Comedication associated with an AE in patients at risk of multi-DDI. Potential outcome is defined as: increase in comedication (↑comedication, associated with a possible impact on safety), decrease in DAA (↓DAA, possible impact on efficacy) and /or increase DAA (↑DAA, associated with a possible impact on safety); ‡Carvedilol also is predicted to increase DAA concentration. No AEs were reported in SOV/VEL-treated patients with potential multi-DDIs within nervous system (0/24) or alimentary (0/49) therapeutic classifications.

- In terms of the indirect measure of DAA effectiveness, new DAA regimens were started within 6 months in:
  - 7 (1.0%) SOF/VEL-treated patients (5/7 showed risk of at least 1 DDI linked to ↓DAA; 1 patient had received ≥2 comedications predicted to ↓DAA)
  - 10 (1.1%) GLE/PIB-treated patients (10/10 showed risk of at least 1 DDI linked to ↓DAA; 3 patients had received ≥2 comedications predicted to ↓DAA)

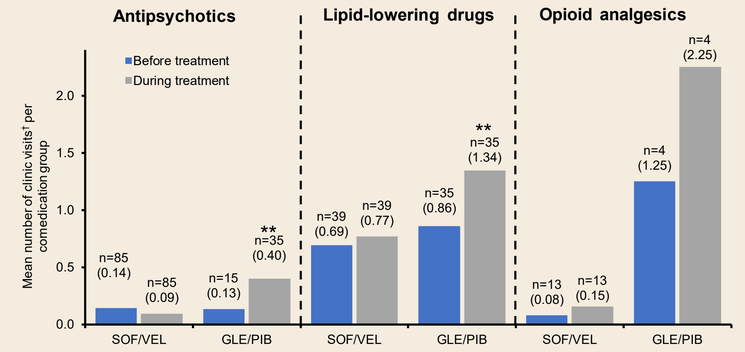
Figure 5: Actions taken during DAA treatment for comedications with potential DDIs



*p<0.05

- A numerically higher number of patients had their co-medications discontinued during DAA treatment in the GLE/PIB treatment group compared with the SOF/VEL treatment group (Figure 5)

Figure 6: Healthcare resource utilisation (specialist visits†) before and during DAA treatment



**p<0.001; †Specialist visits: cardiologist, neurologist, endocrinologist, pneumologist, pain unit, and emergency room; Number of patients: SOF/VEL=137; GLE/PIB=54.

- DDIs resulted in numerically higher mean clinic visits in GLE/PIB-treated patients compared with SOF/VEL-treated patients during DAA treatment in antipsychotics and lipid-lowering drugs (Figure 6)

Conclusions

- In Spain approximately 10% of HCV patients taking two or more comedications are at risk of multi-DDIs with DAAs
- There is a higher risk of increased comedication concentration and AEs in GLE/PIB-treated patients in comparison with SOF/VEL-treated patients
- There was less risk of AEs with antipsychotics and lipid-lowering drugs with SOF/VEL treatment compared with GLE/PIB

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Abbreviations: AASLD, American Association for the Study of Liver Diseases; AE, adverse events; APASL, Asian Pacific Association for the Study of the Liver; DAA, direct-acting antiviral; DDI, drug–drug interaction; EASL, European Association for the Study of the Liver; FIB-4, fibrosis-4; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; PK, pharmacokinetic; SD, standard deviation; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virological response.

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