Global adverse events reported for direct-acting antiviral therapies for the treatment of hepatitis C: an analysis of the World Health Organization VigiBase

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Background Direct-acting antivirals (DAAs) have transformed the treatment of hepatitis C infection (HCV) globally. Exploratory studies to identify potential rare adverse drug events associated with DAAs to optimize their use are scarce.
Objective We aimed to describe the most common serious DAA-associated adverse drug reaction (ADR) reports overall and by DAA regimen.
Methods We conducted a cross-sectional analysis of post-market ADRs associated with DAA therapy using VigiBase, the global database of the WHO Programme for International Drug Monitoring. Reports occurring between 2013 and 2020 in which an eligible DAA brand or regimen was reported as the suspect drug were included and described. Reports of concomitant ribavirin or interferon use were excluded. The top 25 events for all reports where the outcome was indicated as 'serious' or 'life-threatening' were described overall and by drug regimen.
Results We identified 56 636 global ADR reports [45% women, 38% ledipasvir/sofosbuvir use, 67% from USA/Canada, average patient age 57 (SD 13) years]. Overall, 3.8% of reports described a life-threatening event or death. Unexpected ADRs included major pulmonary (dyspnea, pneumonia, and respiratory failure) and cardiac (myocardial infarction and cardiac arrest) events.
Comment When examining all serious ADRs for DAAs globally, unexpected pulmonary and cardiac events were identified and may be of interest for further research on DAA safety. Future studies must examine population-level risk of ADRs for DAA therapies while accounting for confounding by indication, comorbidities, and stage of HCV disease. Eur J Gastroenterol Hepatol 33: e1017–e1021

Introduction

Direct-acting antivirals (DAAs) for the treatment of hepatitis C (HCV) have demonstrated sustained virologic response rates in 90% of patients and have greatly lessened the burden of HCV disease globally [1]. Since sofosbuvir was approved as the first DAA in 2013, numerous other DAAs have come to market, with new mechanisms of action, combinations, and genotype activity, broadening their clinical indications and expanding use worldwide. While 71 million persons have been diagnosed with HCV infection and over five million patients have been treated with DAAs globally [2], studies to identify potential rare adverse drug reactions (ADRs) are scarce.

Clinical trials identified few serious ADRs associated with DAAs, and so DAAs are considered generally safe [2]. However, trials are limited in their ability to detect rare ADRs due to power limitations and are often suboptimal for identifying ADRs that occur in 'real-world' conditions due to trial inclusion criteria. For example, some patients receiving DAA therapy in practice may have more comorbidities, previous HCV treatment, or be of older age than those included in studies from which safety data are derived. Therefore, postmarketing surveillance is essential to identify potential safety signals.

DAAs are critical for patient care, yet exploration of potential rare ADRs for future study is important to identify if some patients may benefit from treatment with one DAA over another, or if additional monitoring during therapy is needed. Thus, on a global scale, we aimed to describe ADR reports of DAA therapies overall, and by regimen. Additionally, we identified the top 25 adverse events potentially associated with DAA therapy among reports where the outcome was classified as serious or life-threatening.

Methods

We performed a cross-sectional analysis using VigiBase, the global database of the WHO Programme for International

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Table 1. Characteristics of reports associated with novel direct-acting antiviral agents for Hepatitis C identified through the WHO VigiBase, 1 January 2013 to 3 May 2020 (*N* = 56 636)

	Daclatasvir/ sofosbuvir (*N* = 3174)	Daclatasvir/ asunaprevir (*N* = 2230)	Sofosbuvir/ velpatasvir (*N* = 8233)	Ledipasvir/ sofosbuvir (*N* = 21 483)	Glecaprevir/ pibrentasvir (*N* = 8725)	Ombitasvir/ paritaprevir/ritonavir (*N* = 7270)	Sofosbuvir/ velpatasvir/voxila- previr (*N* = 779)	Elbasvir/ grazoprevir (*N* = 4742)	Total (*N* = 56 636)
Mean age (SD) (years)	52.2 (12.2)	64.4 (11.7)	54.5 (12.9)	57.7 (11.7)	53.3 (14)	59.3 (11.6)	58.3 (9.7)	58.3 (9.7)	56.5 (12.6)
Missing age	840 (26.5%)	496 (22.2%)	1846 (22.4%)	5730 (26.7%)	2526 (29.0%)	3782 (52.0%)	210 (27.0%)	1825 (38.5%)	17255 (30.5%)
Female	1405 (44.3%)	1126 (50.5%)	3447 (41.9%)	9062 (42.2%)	3918 (44.9%)	4042 (55.6%)	203 (26.1%)	2049 (43.2%)	25252 (44.6%)
Missing sex	221 (7.0%)	205 (9.2%)	141 (1.7%)	729 (3.4%)	418 (4.8%)	317 (4.4%)	31 (4.0%)	471 (9.9%)	2533 (4.5%)
Consumer-reported	228 (7.2%)	54 (2.4%)	1183 (14.4%)	5107 (23.8%)	1282 (14.7%)	5265 (72.4%)	95 (12.2%)	1422 (30.0%)	14636 (25.8%)
Country of origin									
US/Canada	506 (15.9%)	17 (0.8%)	6554 (79.6%)	16633 (77.4%)	6271 (71.9%)	3864 (53.2%)	591 (75.9%)	3309 (69.8%)	37745 (66.6%)
Europe	897 (28.3%)	9 (0.4%)	1365 (16.6%)	2930 (13.6%)	1954 (22.4%)	2896 (39.8%)	150 (19.3%)	1140 (24.0%)	11341 (20.0%)
Egypt	1219 (38.4%)	0 (0%)	0 (0%)	33 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1252 (2.2%)
Australia	360 (11.3%)	0 (0%)	103 (1.3%)	166 (0.8%)	13 (0.2%)	8 (0.1%)	16 (2.1%)	21 (0.4%)	687 (1.2%)
Japan	2 (0.1%)	806 (36.1%)	22 (0.3%)	1172 (5.5%)	307 (3.5%)	0 (0%)	0 (0%)	0 (0%)	2309 (4.1%)
South Korea	54 (1.7%)	1346 (60.4%)	0 (0%)	153 (0.7%)	77 (0.9%)	95 (1.3%)	0 (0%)	208 (4.4%)	1933 (3.4%)
Other	136 (4.3%)	52 (2.3%)	189 (2.3%)	396 (1.8%)	103 (1.2%)	407 (5.6%)	22 (2.8%)	64 (1.4%)	1369 (2.4%)
Seriousness criteria of outcome									
Death	107 (3.4%)	89 (4.0%)	260 (3.2%)	817 (3.8%)	185 (2.1%)	144 (2.0%)	15 (1.9%)	93 (2.0%)	1710 (3.0%)
Life-threatening	47 (1.5%)	29 (1.3%)	34 (0.4%)	208 (1.0%)	50 (0.6%)	60 (0.8%)	8 (1.0%)	39 (0.8%)	475 (0.8%)

Drug Monitoring [3]. VigiBase compiles individual post-market case safety reports (henceforth 'reports') from over 130 countries. Reports include patient demographics, ADRs coded according to the Medical Dictionary for Regulatory Activities (MedDRA), and medications used before and at the time point of the ADR per the reporter.

We identified all reports from 1 January 2013 to 3 May 2020 (data extraction date) that reported an approved DAA brand or regimen as the suspect drug. The DAA regimens and combinations for the treatment of HCV that were included in the search of VigiBase were daclatasvir, sofosbuvir (Daklinza and Sovaldi); daclatasvir, asunaprevir (Daklinza and Sunvepra); sofosbuvir/velpatasvir (Epclusa); ledipasvir/sofosbuvir (Harvoni); glecaprevir/pibrentasvir (Maviret); ombitasvir/paritaprevir/ritonavir (ViekiraPak); sofosbuvir/velpatasvir/voxilaprevir (Vosevi); and elbasvir/grazoprevir (Zepatier). Reports related to DAA regimens that were off-market on the date of data extraction (i.e. boceprevir, simeprevir, or telaprevir) were excluded. We also excluded any reports that included ribavirin or interferon as concurrent medications, regardless of whether they were classified as a suspect or nonsuspect drug. Finally, while we excluded reports that identified sofosbuvir alone or daclatasvir alone as the suspect drug from the primary analysis because these drugs were never approved as monotherapies, we included these reports in a secondary analysis.

We first described the frequency and proportion of patient characteristics, report characteristics, and ADR serious criteria overall and by DAA regimen. From all reports associated with DAAs combined that were flagged with the seriousness criteria 'death' or 'life-threatening', we identified the 25 most frequently reported events, which were recorded as MedDRA Preferred Terms (MedDRA). We then identified the frequency and proportion of these adverse events among reports associated with DAA therapy, overall and stratified by DAA regimen. Adverse events were described as expected or unexpected based on whether they were previously reported in trials. Multiple outcomes could be associated with each report, and therefore ADRs were not mutually exclusive. We performed all analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA). The data used only contained anonymized and aggregated clinical information and thus this project was determined to be exempt from research ethics board approval.

Results

We identified 56 636 eligible reports for the primary analysis (Table 1 and Supplemental Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A691*). The average age for patients was 57 (SD 13) years, and 45% were women (31% missing age and 5% missing sex information). Most reports (67%) originated from the USA and Canada, and the majority (38%) were for ledipasvir/sofosbuvir. Overall, 3.8% (N = 2185) of reports were for serious ADRs (3.0% for death, 0.8% for life-threatening events). The proportion of fatal outcomes ranged from a low of 1.9% with sofosbuvir/velpatasvir/voxilaprevir to a high of 4.0% among reports for daclatasvir/asunaprevir. In the secondary analysis, 3671 reports included sofosbuvir or daclatasvir alone as the suspect drug (Supplemental Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A691*), for a total of 60 307 reports associated with DAAs. Trends in patient demographics or region of reporting were unchanged when these reports were included.

The proportion of adverse events by DAA regimen is presented in Table 2. Expected ADRs among these were fatigue (19.7%), malaise (1.1%), nausea (8.2%), diarrhea (4.7%), vomiting (2.8%), sepsis (0.3%), and hepatic/renal events [acute kidney injury (0.7%), renal failure (0.3%)]. Unexpected ADRs included pulmonary events [dyspnea (1.5%), pneumonia (0.9%), respiratory failure (0.1%)] and cardiovascular events [myocardial infarction (0.3%), and cardiac arrest (0.1%), or cardiorespiratory arrest (0.1%)]. The proportion of these serious ADRs among all reported events differed between regimens. Medications with the highest proportion of cardiovascular events were ledipasvir/sofosbuvir (0.7%) and ombitasvir/paritaprevir/ritonavir (0.6%), and the highest proportion with pulmonary events were daclatasvir/sofosbuvir (3.3%) and ombitasvir/paritaprevir/ritonavir (3.2%). However, some variation

Table 2. Adverse events associated with novel direct-acting antiviral agents for Hepatitis C identified through the WHO VigiBase, 1 January 2013 to 3 May 2020 (*N* = 56 636)

	Daclatasvir/ sofosbuvir (*N* = 3174)	Daclatasvir/ asunaprevir (*N* = 2230)	Sofosbuvir/ velpatasvir (*N* = 8233)	Ledipasvir/ sofosbuvir (*N* = 21 483)	Glecaprevir/ pibrentasvir (*N* = 8725)	Ombitasvir/ paritaprevir/ritonavir (*N* = 7270)	Sofosbuvir/ velpatasvir/voxil- aprevir (*N* = 779)	Elbasvir/ grazoprevir (*N* = 4742)	Total (56 636)
Asthenic conditions`									
Fatigue	82 (2.6%)	342 (15.3%)	1938 (23.5%)	4275 (19.9%)	2131 (24.4%)	1246 (17.1%)	149 (19.1%)	1019 (21.5%)	11,182 (19.7%)
Asthenia	30 (0.9%)	49 (2.2%)	182 (2.2%)	483 (2.2%)	199 (2.3%)	450 (6.2%)	11 (1.4%)	104 (2.2%)	1508 (2.7%)
Malaise	11 (0.3%)	20 (0.9%)	88 (1.1%)	251 (1.2%)	76 (0.9%)	103 (1.4%)	8 (1%)	59 (1.2%)	616 (1.1%)
Nausea and vomiting symptoms; diarrhea (excluding infective)									
Nausea	55 (1.7%)	114 (5.1%)	837 (10.2%)	1347 (6.3%)	908 (10.4%)	815 (11.2%)	83 (10.7%)	479 (10.1%)	4638 (8.2%)
Diarrhea	66 (2.1%)	78 (3.5%)	463 (5.6%)	926 (4.3%)	399 (4.6%)	399 (5.5%)	70 (9%)	288 (6.1%)	2689 (4.7%)
Vomiting	25 (0.8%)	54 (2.4%)	215 (2.6%)	518 (2.4%)	243 (2.8%)	386 (5.3%)	24 (3.1%)	141 (3%)	1606 (2.8%)
Breathing abnormalities, respiratory failures, lower respiratory tract infections									
Dyspnea	9 (0.3%)	50 (2.2%)	90 (1.1%)	325 (1.5%)	111 (1.3%)	167 (2.3%)	13 (1.7%)	73 (1.5%)	838 (1.5%)
Pneumonia	47 (1.5%)	19 (0.9%)	66 (0.8%)	190 (0.9%)	79 (0.9%)	53 (0.7%)	6 (0.8%)	36 (0.8%)	496 (0.9%)
Respiratory failure	2 (0.1%)	4 (0.2%)	7 (0.1%)	33 (0.2%)	7 (0.1%)	18 (0.2%)	0 (0%)	5 (0.1%)	76 (0.1%)
Gastrointestinal and abdominal pains (excluding oral and throat pain)									
Abdominal pain	31 (1%)	165 (7.4%)	98 (1.2%)	235 (1.1%)	141 (1.6%)	136 (1.9%)	9 (1.2%)	96 (2%)	911 (1.6%)
Renal failure and impairment									
Acute kidney injury	17 (0.5%)	43 (1.9%)	28 (0.3%)	219 (1%)	27 (0.3%)	48 (0.7%)	1 (0.1%)	14 (0.3%)	397 (0.7%)
Renal failure	5 (0.2%)	14 (0.6%)	13 (0.2%)	89 (0.4%)	19 (0.2%)	39 (0.5%)	1 (0.1%)	15 (0.3%)	195 (0.3%)
Ischemic coronary artery disorders; ventricular arrhythmias and cardiac arrest									
Myocardial infarction	2 (0.1%)	5 (0.2%)	22 (0.3%)	83 (0.4%)	27 (0.3%)	13 (0.2%)	0 (0.0%)	9 (0.2%)	161 (0.3%)
Cardiac arrest	3 (0.1%)	6 (0.3%)	9 (0.1%)	38 (0.2%)	6 (0.1%)	12 (0.2%)	0 (0.0%)	5 (0.1%)	79 (0.1%)
Cardio-respiratory arrest	1 (0%)	1 (0%)	2 (0%)	25 (0.1%)	0 (0.0%)	13 (0.2%)	0 (0.0%)	2 (0%)	44 (0.1%)
Sepsis, bacteremia, viremia, and fungemia									
Sepsis	11 (0.3%)	13 (0.6%)	21 (0.3%)	61 (0.3%)	15 (0.2%)	11 (0.2%)	1 (0.1%)	12 (0.3%)	145 (0.3%)
Septic shock	1 (0%)	5 (0.2%)	7 (0.1%)	27 (0.1%)	5 (0.1%)	3 (0%)	1 (0.1%)	1 (0.0%)	50 (0.1%)
Other									
Multiple organ dysfunction syndrome	0 (0.0%)	4 (0.2%)	5 (0.1%)	15 (0.1%)	1 (0.0%)	5 (0.1%)	2 (0.3%)	2 (0.0%)	34 (0.1%)
Hepatic symptoms (grouped by MedDRA higher-level terms)[a]									
Hepatic neoplasms, malignant[a]	44 (1.4%)	69 (3.1%)	44 (0.5%)	571 (2.7%)	38 (0.4%)	21 (0.3%)	19 (2.4%)	10 (0.2%)	816 (1.4%)
Hepatobiliary signs and symptoms	48 (1.5%)	20 (0.9%)	53 (0.6%)	241 (1.1%)	57 (0.7%)	80 (1.1%)	6 (0.8%)	28 (0.6%)	533 (0.9%)
Hepatic failure and associated disorders	45 (1.4%)	23 (1%)	31 (0.4%)	205 (1%)	35 (0.4%)	60 (0.8%)	2 (0.3%)	14 (0.3%)	415 (0.7%)
Hepatic fibrosis and cirrhosis	18 (0.6%)	30 (1.3%)	42 (0.5%)	204 (0.9%)	59 (0.7%)	41 (0.6%)	11 (1.4%)	22 (0.5%)	427 (0.8%)
Hepatic vascular disorders	21 (0.7%)	9 (0.4%)	23 (0.3%)	113 (0.5%)	28 (0.3%)	19 (0.3%)	7 (0.9%)	4 (0.1%)	224 (0.4%)

Adverse events were identified by selecting the top 25 reported events among patients where the seriousness criteria were recorded as "death" or "life-threatening" to identify outcomes of clinical interest. Frequencies of the top 25 outcomes (MedDRA preferred terms) were then identified among all case reports. Multiple outcomes may be reported in a single report.

MedDRA, Medical Dictionary for Regulatory Activities.

[a]Encompasses hepatic-related terms in the top 25 MedDRA Preferred Terms (ascites, hepatic cancer, hepatocellular carcinoma, hepatic cirrhosis, hepatic encephalopathy, hepatic failure, esophageal varices hemorrhage).

was observed between medications in the proportion of types of events within these categories [i.e. highest proportion of reports for dyspnea (ombitasvir/paritaprevir/ritonavir: 2.3%), pneumonia (daclatasvir/sofosbuvir: 1.5%), myocardial infarction (ledipasvir/sofosbuvir: 0.4%)]. Finally, the proportion of reports with death recorded ranged between 2.0% (elbasvir/grazoprevir) and 5.4% (valpatasvir/sofosbuvir). The secondary analysis of 60 307 reports including sofosbuvir or daclatasvir alone showed similar results (Supplemental Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A691*).

Discussion

Our analysis of over 56 000 case safety reports with DAAs identified that the most commonly reported adverse events were mild and previously known, including fatigue, diarrhea, and nausea. However, serious adverse events that were not previously reported in clinical trials [4–6] were identified, including major cardiovascular events. Additionally, differences in the reporting of serious adverse events were identified between different regimens, highlighting the need for further real-world evidence on the safety and comparative safety of DAAs.

Unexpected reporting of serious pulmonary and cardiovascular events is of interest. Major cardiac events have been rarely reported in clinical trials; however, bradyarrhythmia, a potential precursor to cardiac arrest, has been associated with DAA therapies including sofosbuvir when in combination with amiodarone [7,8]. In addition, a review and meta-analysis of DAA trials identified an increased risk of thrombotic events associated with DAAs

[4], potentially secondary to hepatic effects. Whether true risk of all cardiovascular events, both cardiac arrest and thrombotic incidents, is elevated with DAA treatment remains unknown. Regarding pulmonary effects, dyspnea has been reported with ledipasvir/sofosbuvir use [9,10], and one examination of U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) data identified pneumonia among the top 25 reported adverse events for DAA treatments [6]. Drug-induced lung injury has also been associated with DAA therapy in case reports [11,12]; however, we are unaware of established associations of respiratory arrest with any DAA therapy, and pneumonia was not identified as a side effect in clinical trials.

Our report also showed differences in the prevalence of ADRs between DAA regimens that require further exploration. For example, though few in number, pneumonia reports constituted a substantially larger portion of reports for daclatasvir/sofosbuvir combination treatment versus other therapies, and ledipasvir/sofosbuvir combination therapy showed highest proportion of myocardial infarction reports. To date, little real-world evidence has explored the association between DAAs and respiratory and cardiovascular events. Huang and colleagues did find that in one electronic health record database that pneumonia was more frequently reported among DAAs approved since 2013 [6], yet this trend was not observed in their examination of FAERS data nor in our study's results. In future research, DAA regimens should be directly compared for safety, accounting for differences in prognostic factors between patients taking different DAAs.

To our knowledge, ours is the first study to describe global reported ADRs of DAAs overall and by DAA regimen, and is the largest postmarket study of DAA safety to date. However, there are important limitations to the use of pharmacovigilance data that should be considered when interpretating the results. ADR reporting is passive and cross-sectional in nature and therefore cannot provide a measurement of true risk, association, or information about temporality of events in relation to DAA exposure. Issues of missing data and reporting bias in ADR databases, including the WHO VigiBase, are well-established [13]. In addition, unknown adverse events are likely underreported as compared to known adverse events due to observation bias. Similarly, medications with more widespread use and use in diverse populations (i.e. ledipasvir/sofosbuvir) may also be more likely to be related to adverse events. Furthermore, reporting also relies on the health literacy of the reporter, who may be a consumer (ranging from 2.4% to 72.4% of reports in this study). Due to database limitations, we were unable to examine patients' comprehensive medical history, including current HCV stage, phenotype, comorbidities, or concurrent medications, that may all affect true risk of the observed events. Moreover, though it is possible to report prior medication use in ADRs, it is rarely done. Thus, the results should be interpreted as exploratory signal detection and not as validation or testing a causal hypothesis. The safety signals identified can serve as a starting point for rigorous, longitudinal research with appropriate comparator groups; future studies must examine population-level risk of ADRs, comparative safety, and potential drug–drug interactions of DAAs while accounting for confounding by indication, comorbidities, and stage of HCV disease.

In conclusion, our global examination of ADRs reported with DAA therapy identified unexpected ADRs, notably respiratory and cardiovascular events, with potential differences between DAA regimens. Our results call for population-based, longitudinal research of the risk of serious ADRs with DAA therapy, specifically between DAA regimens and among high-risk subgroups. Understanding the true risk of DAA adverse effects and potential mechanisms in real-world settings is needed to guide clinical decision-making between the many options available today for DAA therapy for HCV.

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Conflicts of interest

S.W. is a member of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and a member of the Human Medicines Expert Committee (HMEC) of Swissmedic. The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of an agency, competent authority or any committees or working parties. K.N.H. and M.T. report grants from the Canadian Institutes of Health Research (CIHR) outside of this work. The information presented in this work does not represent the opinion of the Uppsala Monitoring Centre or the WHO. For the remaining authors, there are no conflicts of interest.

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