Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Original article | Published 12 May 2021 | doi:10.4414/smw.2021.20503
Cite this as: Swiss Med Wkly. 2021;151:w20503

Drug-induced liver injury in Switzerland: an analysis of drug-related hepatic disorders in the WHO pharmacovigilance database VigiBase™ from 2010 to 2020

Ortland Imke[a], Mirjalili Mahtabalsadat[b], Kullak-Ublick Gerd A.[a], Peymani Payam[ac]

[a] Department of Clinical Pharmacology and Toxicology, University Hospital Zurich (USZ), University of Zurich (UZH), Switzerland
[b] Department of Clinical Pharmacy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[c] Health Policy Research Centre, Institute of Heath, Shiraz University of Medical Sciences, Shiraz, Iran

Summary

AIMS OF THE STUDY: Our aim was to explore drug-induced liver injury (DILI) in Switzerland using the real-world data of the global pharmacovigilance database VigiBase™, with a special focus on the new drug class of checkpoint inhibitors. This is the first study investigating drug-related hepatic disorders in Switzerland in a global pharmacovigilance database.

METHODS: This was a retrospective study analysing the ICSRs (individual case safety reports) of the global pharmacovigilance database VigiBase™. We explored all ICSRs submitted in Switzerland within the last 10 years (1 July 2010 to 30 June 2020). For data extraction, the standardised MedDRA query (SMQ) "narrow drug-related hepatic disorders – severe events only" was applied. The ICSRs, drug-reaction pairs and adverse drug reactions were analysed descriptively, including a special focus on checkpoint inhibitors. For comparing the hepatic adverse drug reactions of pembrolizumab, nivolumab and ipilimumab, the reporting odds ratios (RORs) were calculated in a disproportionality analysis.

RESULTS: In total, 2042 ICSRs could be investigated, comprising 10,646 drugs and 6436 adverse drug reactions. Gender was equally distributed between male and female. Patients were on average 57 years old. The mortality rate was high, with fatal adverse reactions in over 10% of cases. On average, patients used five drugs including two suspected drugs. Paracetamol, amoxicillin/clavulanic acid, esomeprazole and atorvastatin ranked among the most frequently suspected drugs for severe drug-related hepatic disorders. However, Vigibase™ data are not appropriate for judging causality and these results should be interpreted with caution owing to the possible influences of comedication or comorbidity. An average of three adverse drug reactions per ICSR were reported, most frequently including hepatocellular injury, cholestatic liver injury, and liver injury. For checkpoint inhibitors, hepatitis was the most frequently reported hepatic adverse drug reaction. In comparison with nivolumab and ipilimumab, pembrolizumab had a significantly higher ROR for hepatitis (2.41, p = 0.016), but also a lower ROR for autoimmune hepatitis (0.11, p = 0.009).

CONCLUSION: Our findings highlight the importance for healthcare providers in Switzerland to pay special attention to possible drug-induced liver injuries because of their high mortality rate. The analysis of real-world data confirms the previous assumption that hepatitis is the most frequent hepatic adverse event for checkpoint inhibitors. Further clinical studies are warranted to directly compare hepatic adverse drug reactions to different checkpoint inhibitors.

Correspondence:
Gerd A. Kullak-Ublick, MD, Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Rämistrasse 100, CH-8091 Zürich, gerd.kullak[at]usz.ch

Introduction

Hepatic adverse drug reactions are an important issue in drug safety: DILI (drug-induced liver injury) is the leading cause of acute liver failure in the United States and Europe [1, 2]. The consequences may be severe: it was estimated that within 6 months of onset of DILI, almost 10% of patients undergo liver transplantation or die, and nearly 20% may suffer persistent liver injuries [3]. Furthermore, DILI is considered one of the most common causes of compound attrition in drug development and for withdrawal of drugs from the market [4]. The diagnosis and management of DILI is challenging since, due to the lack of specific biomarkers, the diagnosis primarily relies on the exclusion of other causes [4, 5].

Because of the frequency and severity of hepatic adverse drug reactions, cautious monitoring is crucial. Because of the limited predictive value of pre-clinical assays and the limited power of pre-marketing clinical trials to detect rare safety and toxicity issues, large drug registries and spontaneous reporting systems of adverse drug reactions have a critical role in the early identification of safety signals, especially for rare idiosyncratic events such as DILI. VigiBase™, the World Health Organization (WHO) global in-

dividual case safety report database, is among the world's largest spontaneous adverse event reporting systems and has been used for DILI research in various studies [6–8]. Early detection of drug-related hepatic disorders via spontaneous reporting systems is especially important for new drugs. Checkpoint inhibitors are a new therapeutic class that has been increasingly used in oncology during recent years. There has been emerging evidence of immune-related hepatic adverse events with checkpoint inhibitors [9]. Analyses of real-world data may complement the existing knowledge about DILI in this new drug class.

Our aim was to explore drug-related hepatic disorders in Switzerland using the real-world data of the global VigiBase™ database, with a special focus on the new drug class of checkpoint inhibitors. Other studies have explored hepatotoxicity using pharmacovigilance data from VigiBase™ [6, 8]; however, to the best of our knowledge, this is the first study investigating DILI in a global spontaneous reporting system with a focus on Switzerland. This regional focus is of high interest because data from other countries may not necessarily be applicable to Switzerland. Furthermore, this study fills a gap in knowledge, using real-world data to investigate the question of whether checkpoint inhibitors differ in terms of their hepatic safety profile.

Methods

Study design

This was a retrospective study of registry data, analysing the ICSRs (individual case safety reports) of the global pharmacovigilance database VigiBase™ regarding severe drug-related hepatic disorders in Switzerland from 2010 to 2020. The analysis also particularly focused on severe liver disorders involving the new therapeutic class of checkpoint inhibitors.

VigiBase™ is an international database of the WHO comprising more than 20 million anonymised reports of adverse drug reactions [10]. However, as a registry database without further access to clinical data, the individual causal relationship between a suspected adverse drug reaction and a medicinal product cannot be formally assessed through these data. The ICSRs were retrieved from VigiBase™ via the software VigiLyze™. For extraction of the ICSRs with drug-related hepatic disorders, an appropriate standardised MedDRA query (SMQ) was used, because these queries are validated standard sets of MedDRA (Medical Dictionary for Regulatory Activities) terms, which undergo extensive reviewing and testing [11]. In order to focus on DILI with high clinical impact, the SMQ "narrow drug-related hepatic disorders – severe events only" was applied. We investigated all ICSRs submitted in Switzerland within the last 10 years (1 July 2010 to 30 June 2020). Since the VigiBase™ database includes anonymised data only, ethics approval of the study was not required. The reported drugs were analysed according to the WHO drug active ingredient and concomitant as well as suspected drugs were separately reviewed. MedDRA preferred terms were used for analysing the adverse drug reactions.

Data adjustment

For removing duplicates, the automated vigiMatch algorithm was applied and a de-duplicated dataset was extracted from VigiBase™. Additionally, the dataset was systematically screened by manually searching for further duplicates of the ICSRs, the drug-reaction pairs and the adverse drug reactions. Suspected duplicates were removed from the dataset. Regarding the duration of events or drug application, all data where only the year was stated were not included into the respective analysis. Where multiple reporters of the ICSR were indicated, only the most "competent" reporter (for instance physician > laymen) was taken into account. Similarly, only the most serious outcome (e.g., death > hospitalisation) was considered if different seriousness criteria were given. All records with uncoded and therefore unknown active ingredients were eliminated.

Statistical analysis

The ICSRs, drug-reaction pairs, and adverse drug reactions were analysed descriptively. A disproportionality analysis calculating the reporting odds ratio (ROR) compared the hepatic adverse drug reactions of the three most frequently used checkpoint inhibitors, namely pembrolizumab, nivolumab, and ipilimumab. The ROR is the odds of a certain suspected adverse drug reaction occurring with a certain substance, compared with the odds of the same reaction occurring with all other substances in the database [12]. For enhancing clinical relevance, only the reactions associated with hepatic dysfunction were considered in the disproportionality analysis; reactions such as myocarditis or thyroiditis were excluded. For comparing the RORs of the checkpoint inhibitors, a two-sided Fisher's exact test was used. The 95% confidence intervals were computed and p-values <0.05 were considered statistically significant.

The statistical analyses were performed using Microsoft Excel© 2016 (Microsoft Corporation, Redmond, WA, USA) and SPSS© 26.0 for Windows (IBM Corporation, Armonk, USA).

Results

Data extraction

The de-duplicated dataset for the SMQ "narrow drug-related hepatic disorders – severe events only" in the period from 1 July 2010 to 30 June 2020 included 149,867 ICSRs when all countries were considered. The United States of America reported the highest percentage of severe drug-related hepatic disorders, with 48,823 cases (32.6%) submitted during the last 10 years. The highest number of ICSRs reported by European countries was from France (19,109; 12.8%), followed by Germany (7950; 5.3%). A total of 2050 case reports (1.4%) were submitted in Switzerland. The manual search for additional duplicates, identified eight redundant cases among the ICSRs reported in Switzerland. Thus, in total 2042 cases could be analysed, comprising 10,646 drugs and 6436 drug-reaction pairs (fig. 1). The comprehensive SMQ on drug-related hepatic disorders – which was not restricted to severe events only – comprised a total of 3765 de-duplicated cases for the last 10 years in Switzerland.

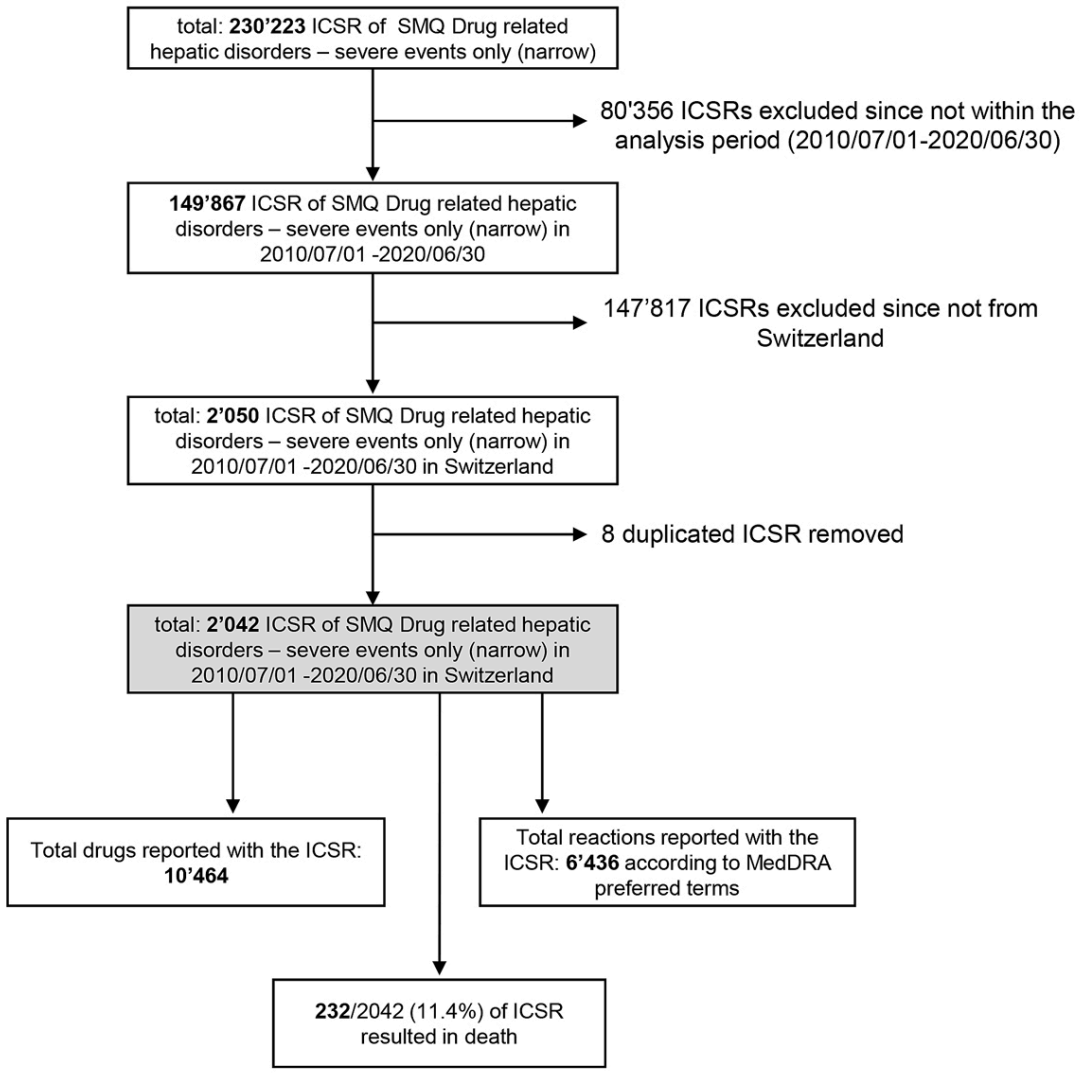
Individual case safety reports (ICSRs)

In the 2042 ICSRs analysed, the patients' gender was equally distributed between male and female (female 989, 48.4%; male 946, 46.3%; unknown 107, 5.2%). Patients were on average 57 years old (standard deviation 19.5 years; maximum 98 years). In total, 762 ICSRs reported the patients' age; 39.0% (687/1762) of the ICSRs concerned elderly patients (≥65 years) and only 3.6% (63/1762) children or adolescents (<18 years). Because we aimed at focusing on clinically relevant cases utilising the SMQ with "severe events only", most ICSR cases were classified as serious: In total, 86.4% (1765/2042) cases were categorised as serious, and only 6.1% (125/2042) were judged to be non-serious. For 7.4% (152/2042), seriousness was unknown. The majority of cases were serious because they either caused or prolonged hospitalisation (730/2042, 35.7%) or for "other medically important reasons" (712/2042, 34.9%). Furthermore, 5.2% (106/2042) of the case reports were categorised as life-threatening and 12/2042 (0.6%) were judged as disabling or incapacitating. For 279/2042 ICSRs, the seriousness criterion remained unknown. The mortality rate was high, with fatal adverse reactions in over 10% of cases (11.4%, 232/2042). The vast majority of ICSRs was reported by physicians (1664/2042, 81.5%). Moreover, 6.2% of cases (127/2042) were reported by pharmacists and 6.2% (127/2042) by other health professionals. Consumers or non-health professionals accounted for only 2% (40/2042) of ICSRs. For 84/2042 case reports, the reporter remained unknown. Table 1 indicates the specified seriousness criteria by gender, age group and reporter.

Frequently reported suspected and concomitant drugs

In total, 10,464 WHO drug active ingredients were reported in the ICSRs. Of these active ingredients, more than one third were suspected of causing the adverse reaction (41.4%; 4331/10,464). More than half of the drugs were reported as concomitant (57.0%, 5966/10,464), whereas only 1.6% of the reported medications were stated to be inter-

Figure 1: Flow chart of VigiBase™ analysis for SMQ "drug-related hepatic disorders – only severe events (narrow)", de-duplicated dataset; ICSR = individual case safety report, MedDRA = Medical Dictionary for Regulatory Activities.



acting (167/10,464). On average, patients used five drugs, including a mean number of two suspected drugs and three concomitant or interacting drugs. In terms of the suspected drugs, the most frequently reported were paracetamol, amoxicillin / clavulanic acid, esomeprazole and atorvastatin (table 2). The most frequently involved drugs, disregarding the causality assessment, are given in table S1 in the appendix.

Data regarding the indication for the reported drugs were sparse. For most drugs, the indication remained unknown. For 6739/10,646 drugs (64.4%), the indication was not given at all and for 9% of the drugs where an indication was given, it was stated that the drug was applied "for unknown indication". Interestingly, the most frequently documented indication was "hepatocellular carcinoma". For all reported drugs, most were administered orally (4838/10,646), followed by intravenous administration (877/

Table 1: Seriousness criteria by gender, age group and reporter.

	Sex			Age class			Reporter				
Seriousness criteria	**Female**	**Male**	**Unknown**	**Younger (<65 years)**	**Elderly (≥65 years)**	**Unknown**	**Non-health professional**	**Other health professional**	**Pharmacist**	**Physician**	**Unknown**
Caused/prolonged hospitalisation	370 (50.7%)	348 (47.7%)	12 (1.6%)	406 (55.6%)	286 (39.2%)	38 (5.2%)	0 (0.0%)	34 (4.7%)	60 (8.2%)	616 (84.4%)	20 (2.7%)
Death	86 (42.4%)	107 (52.7%)	10 (4.9%)	81 (39.9%)	92 (45.3%)	30 (14.8%)	3 (1.5%)	21 (10.3%)	16 (7.9%)	161 (79.3%)	2 (1.0%)
Disabling/incapacitating	8 (66.7%)	4 (33.3%)	0 (0.0%)	5 (41.7%)	5 (41.7%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	11 (97.7%)	0 (0,0%)
Life threatening	65 (61.3%)	39 (36.8%)	2 (1.9%)	75 (70.8%)	28 (26.4%)	3 (2.8%)	1 (0.9%)	7 (6.6%)	11 (10.4%)	85 (80.2%)	2 (1.9%)
Other medically important	312 (43.8%)	327 (45.9%)	73 (10.3%)	346 (48.6%)	185 (26.0%)	181 (25.4%)	31 (4.4%)	61 (8.6%)	29 (4.1%)	574 (80.6%)	17 (2.4%)
Unknown	148 (53.0%)	121 (43.4%)	10 (3.6%)	162 (58.1%)	91 (32.6%)	26 (9.3%)	5 (1.8%)	4 (1.4%)	10 (3.6%)	217 (77.8%)	43 (15.4%)

Table 2: Most frequent suspected and concomitant drugs.

	ATC code	**Frequency**	**Percent of drugs**	**Percent of ICSRs**
Suspected drugs				
Paracetamol	N02BE01	250	5.8	12.2
Amoxicillin / clavulanic acid	J01CR02	134	3.1	6.6
Esomeprazole	A02BC05	85	2.0	4.2
Atorvastatin	C10AA05	84	1.9	4.1
Ibuprofen	M01AE01	61	1.4	3.0
Ceftriaxone	J01DD04	57	1.3	2.8
Rivaroxaban	B01AF01	56	1.3	2.7
Nivolumab	L01XC17	55	1.3	2.7
Pantoprazole	A02BC02	53	1.2	2.6
Sorafenib	L01XE05	53	1.2	2.6
Sulfamethoxazole/trimethoprim	J01EE01	47	1.1	2.3
Methotrexate	L01BA01	45	1.0	2.2
Others		3351	77.4	
Concomitant drugs				
Acetylsalicylic acid	N02BA01	209	3.5	10.2
Pantoprazole	A02BC02	170	2.8	8.3
Torasemide	C03CA04	151	2.5	7.4
Paracetamol	N02BE01	131	2.2	6.4
Metoprolol	C07AB02	126	2.1	6.2
Esomeprazole	A02BC05	107	1.8	5.2
Prednisone	H02AB07	103	1.7	5.0
Calcium carbonate / cholecalciferol	A12AX	100	1.7	4.9
Levothyroxine	H03AA01	86	1.4	4.2
Metamizole	N02BB02	82	1.4	4.0
Lorazepam	N05BA06	75	1.3	3.7
Atorvastatin	C10AA05	73	1.2	3.6
Cholecalciferol	A11CC	72	1.2	3.5
Amlodipine	C08CA01	68	1.1	3.3
Morphine	N02AA01	59	1.0	2.9
Enoxaparin	B01AB05	58	1.0	2.8
Bisoprolol	C07AB07	57	1.0	2.8
Folic acid	B03BB01	57	1.0	2.8
Others		4182	70.1	

ATC = Anatomical Therapeutic Chemical

10,646; intravenous drip, intravenous not otherwise specified, or intravenous bolus). The suspected drugs were applied for a median duration of 10 days. However, there was wide variability, with a standard deviation of 263 days and a range of 0–5825 days. In 3089/10,464 ICSRs the drugs were withdrawn. However, for 5439/10,646 (51.1%), information on the actions taken was not given, remained unknown, or was deemed "not applicable".

Frequently reported adverse drug reactions

In total, 6436 MedDRA preferred terms were reported, implying an average of three reactions per ICSR. Details regarding the reported adverse drug reactions are presented in table 3. The most frequently documented reactions were hepatocellular injury, cholestatic liver injury and liver injury. Drug-induced liver injury was found in 8.1% of the ICSRs. Hepatic failure and acute hepatic failure were reported less frequently. However, these reactions had a very poor prognosis, with a mortality rate of 44.2% and 32.9%, respectively (see table S2 in the appendix). Most adverse reactions were only temporary: 1804/6436 reactions recovered and 1249/6436 were recovering. However, 759/6436 did not recover, 44/6436 recovered with sequelae and 594/6436 were fatal. The reactions frequently associated with death were hepatic failure (45/6436) and acute hepatic failure (27/6436). For 1986 reactions, the outcome was either indicated as unknown or no information concerning the outcome was given. The median duration of the adverse reactions was 10 days; however, information on duration was sparse and there was a high variability (standard deviation 225.2 days).

In total, four fatal events with the term "drug-induced liver injury" were reported. In one of these ICSRs, a female 69-year-old patient took albendazole (for alveolar echinococcosis), which was suspected to have caused the drug-induced liver injury. Together with the drug-induced liver injury, aplasia, septic shock, jaundice, alopecia and acute renal insufficiency were reported. Candesartan was administered as concomitant medication. Another case report mentioned that methotrexate was suspected of causing DILI. In this ICSR, methotrexate was taken at a dosage of 10 mg daily, presumably a medication error. The case report included other symptoms of methotrexate intoxication such as pancytopenia and gastrointestinal inflammation. In another ICSR, Yervoy® (ipilimumab) and Opdivo® (nivolumab) used for a choroid melanoma were suspected of causing drug-induced liver injury. As well as the DILI, thyroiditis was reported.

Comparison of drug-related hepatic disorders with checkpoint inhibitors

In total, 131 ICSRs indicated checkpoint inhibitors as suspected drugs. In only five ICSRs were checkpoint inhibitors reported as concomitant or interacting drugs. The programmed death-1 (PD-1) antibodies nivolumab and pembrolizumab were reported as suspected in 56 ICSRs (2.7% of all ICSRs) and 30 ICSRs (1.5% of all ICSRs), respectively. Ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitor, was suspected of causing the adverse reaction in 36 ICSRs (1.8% of all ICSRs). The programmed death-ligand 1 (PD-L1) antibodies atezolizumab and durvalumab were suspected in eight and one ICSRs, respectively. In total, for immune checkpoint inhibitors, 352 adverse drug reactions were reported, of which 42 (11.9%) were fatal. For pembrolizumab, 76 reactions were mentioned in total, including 45 reactions associated with hepatic injury. For nivolumab, 163 reactions were documented, of which 73 were related to hepatic disorders. In total, 113 reactions were identified for ipilimumab, including 51 with hepatic involvement. Details regarding the hepatic adverse reactions of checkpoint inhibitors are displayed in table 4.

Table 3: Most frequent (at least 1% of reactions) MedDRA preferred terms concerning cases with reported severe drug-related hepatic disorders.

Adverse drug reaction	Frequency	Percent of reactions	Percent of ICSRs
Hepatocellular injury	294	4.6	14.4
Cholestatic liver injury	258	4.0	12.6
Liver injury	208	3.2	10.2
Jaundice	187	2.9	9.2
Hepatitis	179	2.8	8.8
Drug-induced liver injury	165	2.6	8.1
Mixed liver injury	143	2.2	7.0
Liver disorder	127	2.0	6.2
Hepatic failure	104	1.6	5.1
Ascites	99	1.5	4.8
Nausea	95	1.5	4.7
Pyrexia	91	1.4	4.5
Acute kidney injury	84	1.3	4.1
Acute hepatic failure	82	1.3	4.0
Hepatitis cholestatic	81	1.3	4.0
Hepatic enzyme increased	78	1.2	3.8
Fatigue	67	1.0	3.3
Hepatocellular carcinoma	66	1.0	3.2
Hepatotoxicity	66	1.0	3.2
Diarrhoea	64	1.0	3.2
Pruritus	63	1.0	3.1
Vomiting	62	1.0	3.1
Other	3773	58.6	

MedDRA = Medical Dictionary for Regulatory Activities

Table 4: Frequency and proportion of hepatic adverse reactions reported for pembrolizumab, nivolumab, and ipilimumab as suspected drugs.

Reaction	Frequency	Percent total hepatic reactions
Pembrolizumab (n = 45)		
Hepatitis	21	46.7
Hepatotoxicity	3	6.7
Pruritus	2	4.4
Alanine aminotransferase increased	1	2.2
Aspartate aminotransferase increased	1	2.2
Asthenia	1	2.2
Autoimmune hepatitis	1	2.2
Blood alkaline phosphatase increased	1	2.2
Blood bilirubin increased	1	2.2
Drug-induced liver injury	1	2.2
Fatigue	1	2.2
Gamma-glutamyltransferase increased	1	2.2
Hepatic encephalopathy	1	2.2
Hepatic enzyme increased	1	2.2
Hepatitis cholestatic	1	2.2
Hepatocellular injury	1	2.2
Immune-mediated hepatic disorder	1	2.2
Immune-mediated hepatitis	1	2.2
Jaundice	1	2.2
Liver disorder	1	2.2
Mixed liver injury	1	2.2
Ocular icterus	1	2.2
Total	45	100
Nivolumab (n =73)		
Hepatitis	18	24.7
Autoimmune hepatitis	12	16.4
Drug-induced liver injury	6	8.2
Liver disorder	6	8.2
Hepatic enzyme increased	3	4.1
Hepatic failure	3	4.1
Hepatotoxicity	3	4.1
Immune-mediated hepatitis	3	4.1
Liver transplant rejection	2	2.7
Abdominal pain upper	1	1.4
Ascites	1	1.4
Asthenia	1	1.4
Bile duct stenosis	1	1.4
Cholestasis	1	1.4
Fatigue	1	1.4
Graft versus host disease in liver	1	1.4
Hepatic necrosis	1	1.4
Hepatocellular carcinoma	1	1.4
Hepatocellular injury	1	1.4
Hepatorenal failure	1	1.4
Malaise	1	1.4
Metastases to liver	1	1.4
Mixed liver injury	1	1.4
Pruritus	1	1.4
Transaminases increased	1	1.4
Vomiting	1	1.4
Total	73	100.0
Ipilimumab (n = 51)		
Hepatitis	15	29.4
Autoimmune hepatitis	10	19.6
Drug-induced liver injury	3	5.9
Cholestasis	2	3.9
Confusional state	2	3.9
Immune-mediated hepatitis	2	3.9
Jaundice	2	3.9
Asthenia	1	2.0

Reaction	Frequency	Percent total hepatic reactions
Blood bilirubin increased	1	2.0
Cholestatic liver injury	1	2.0
Disorientation	1	2.0
Fatigue	1	2.0
Hepatic enzyme increased	1	2.0
Hepatocellular injury	1	2.0
Hepatorenal syndrome	1	2.0
Hepatotoxicity	1	2.0
Hypoalbuminaemia	1	2.0
Liver disorder	1	2.0
Liver injury	1	2.0
Metastases to liver	1	2.0
Mixed liver injury	1	2.0
Pruritus	1	2.0
Total	51	100.0

Disproportionality analysis indicated that for pembrolizumab the odds of reporting hepatitis were more than two-fold higher compared with the other two checkpoint inhibitors (ROR 2.41, p = 0.016). In contrast, autoimmune hepatitis was substantially less frequently reported for pembrolizumab than for nivolumab/ipilimumab (ROR 0.11, p = 0.009). For nivolumab and ipilimumab, the disproportionality analysis did not result in statistically significant results for any of the analysed hepatic reactions. However, for nivolumab there was a trend towards higher reporting of liver disorders (ROR 4.21, p = 0.077). For ipilimumab, the odds of reporting autoimmune hepatitis were almost twice as high as for nivolumab or pembrolizumab (ROR 1.97, p = 0.148). Results of the disproportionality analysis are presented in table 5.

Discussion

This retrospective study investigated severe drug-related hepatic disorders submitted from 2010 to 2020 in Switzerland in the international WHO drug safety database VigiBase™. In total, 2042 individual case safety reports (ICSRs) were analysed, comprising 10,646 drugs and 6436 adverse drug reactions. Paracetamol, amoxicillin / clavulanic acid, esomeprazole and atorvastatin were among the most frequently suspected drugs for severe drug-related hepatic disorders. For checkpoint inhibitors, hepatitis was the most frequently reported hepatic adverse drug reaction. In comparison with nivolumab and ipilimumab, pembrolizumab showed significantly higher reporting odds ratios for hepatitis, but lower reporting odds ratios for autoimmune hepatitis.

We aimed to focus only on severe cases because of their higher clinical relevance. However, when interpreting the data, it has to be kept in mind that the comprehensive SMQ on drug-related hepatic disorders, which was not restricted to severe events only, resulted in almost twice as many ICSRs. The focus on severe cases also explains the relatively high mortality rate of over 10%. This finding is in line with a previous, prospective DILI study, which found that 8% of DILI patients had died 6 months after enrolment [13]. However, a possible reporting bias should be considered for this result also, since fatal adverse events may be reported more frequently than less severe events in a spontaneous reporting system. Especially acute hepatic failure and hepatic failure were associated with a very high rate of fatal events in our study. However, despite this high mortality rate, the majority of reported adverse reactions were only temporary.

Frequently reported suspected and concomitant drugs

On average, patients used five drugs, which can be classified as polymedication according to standard definitions. Polymedication may contribute to adverse drug reactions as an additional risk factor. Suzuki et al. showed that comedications influence the frequency of liver injury reporting [14]. In our study, a mean of two drugs were documented as being suspected to cause the respective reaction. This shows the common difficulty of attributing an adverse drug reaction to one single drug. Furthermore, this emphasises that pharmacodynamic effects from different

Table 5: Disproportionality analysis of checkpoint inhibitors pembrolizumab, nivolumab, and ipilimumab for frequent hepatic adverse drug reactions.

	Pembrolizumab vs nivolumab/ipilimumab			Nivolumab vs pembrolizumab/ipilimumab			Ipilimumab vs pembrolizumab/nivolumab		
Reaction	**ROR**	**95% CI**	**p-value**	**ROR**	**95% CI**	**p-value**	**ROR**	**95% CI**	**p-value**
Hepatitis	2.41	1.19–4.90	**0.016**	0.55	0.28–1.07	0.096	0.84	0.41–1.72	0.721
Hepatotoxicity	2.14	0.46–9.97	0.385	0.99	0.21–4.55	1	0.37	0.04–3.18	0.676
Autoimmune hepatitis	0.11	0.01–0.81	**0.009**	1.52	0.63–3.68	0.373	1.97	0.8–4.85	0.148
Drug-induced liver injury	0.29	0.04–2.36	0.293	2.06	0.56–7.58	0.332	0.99	0.25–4.00	1
Hepatic enzyme increased	0.68	0.07–6.27	1	2.01	0.33–12.35	0.653	0.57	0.06–5.24	1
Hepatocellular injury	1.39	0.12–15.67	1	0.65	0.06–7.35	1	1.16	0.1–13.16	1
Immune-mediated hepatitis	0.54	0.06–4.76	1	1.33	0.26–6.8	1	1.16	0.21–6.58	1
Liver disorder	0.38	0.05–3.18	0.683	4.21	0.82–21.28	0.077	0.32	0.04–2.65	0.438

CI = confidence interval; ROR = reporting odds ratio
p-values computed as two-sided Fisher's exact test; p <0.05 presented in bold

substances may sum up and potentiate each other, eventually leading to an adverse drug reaction.

The most frequently reported suspected drugs were paracetamol, amoxicillin / clavulanic acid, esomeprazole and atorvastatin. For all these drugs, hepatic disorders are well known and documented in the Swiss drug information [15]. For paracetamol, liver damage via the toxic metabolite N-acetyl-p-benzoquinoneimine is extensively documented, particularly for overdoses [16]. Whether the ICSRs for paracetamol always included overdoses cannot be thoroughly assessed because of missing information in the spontaneous reporting database. In the literature, amoxicillin/clavulanic acid is currently deemed the most common cause of drug-induced liver disease in most large case series from the United States and Europe [16]. A prospective, multicentric observational study reported 23/300 cases of DILI due to exposure with amoxicillin/clavulanate [13]. The mechanism of amoxicillin/clavulanate-induced hepatotoxicity is still unknown, but an immunoallergic cause is postulated [16].

The high incidence of DILI associated with esomeprazole and atorvastatin is somewhat surprising. The results should be interpreted with caution, since VigiBase™ data are not appropriate for judging causality between drugs and a defined adverse reaction. Comedication or comorbidity need to be considered, since proton-pump inhibitors and statins are commonly used in multi-morbid patients who frequently receive polymedication. Causality assessment of individual case reports could help to clarify the causal relationship between atorvastatin/esomeprazole and DILI. However, a causality assessment is difficult with this type of data. Presumably the high consumption of atorvastatin and esomeprazole rather than the high risk of hepatotoxicity caused these two substances to rank among the most frequently reported suspected drugs associated with DILI. According to the medication report of a leading health insurer in Switzerland, atorvastatin was the 13th most frequently prescribed medicine in Switzerland during 2016–2019. Esomeprazole was not listed, but the proton-pump inhibitor pantoprazole was the 4th most frequently prescribed drug in Switzerland [17]. It has to be emphasised that the overall safety profile of statins and proton-pump inhibitors is good. However, for atorvastatin, periodic monitoring of liver enzymes is advised in the Swiss product label [15] and our real-world data strongly support this recommendation. For esomeprazole, amoxicillin/clavulanic acid, and paracetamol, monitoring of liver parameters is not routinely recommended [15]. However, our data indicate that clinicians' should pay special attention to symptoms of potential liver damage.

Interestingly, paracetamol was not only the most commonly suspected drug in ICSRs related to hepatic disorders, but it was also the fourth most frequent concomitant drug reported. Likewise, esomeprazole and atorvastatin were not only documented among the most frequently suspected drugs, but also among the most frequent concomitant drugs. The differing causality assessments of the substances may be explained by the temporal relationships or de-/rechallenges. However, this additional information is generally not available in the extracted VigiBase™ ICSRs. Of note, "hepatocellular carcinoma" was apparently a frequent indication for the reported drugs, providing a possible alternative explanation for certain hepatic disorders.

Frequently reported adverse drug reactions

Hepatocellular injury (14.4% of ICSRs), cholestatic liver injury (12.69%) and liver injury (10.2%) ranked among the most frequently reported adverse drug reactions. Interestingly, all those terms describe rather nonspecific, general diagnoses for hepatic disorders. In 8.1% of ICSRs, the liver injury was explicitly stated to be drug induced. Of note, in those cases where drugs were explicitly stated to have caused the liver injury, the prognosis was rather positive, with a mortality rate of only 2.4%; the vast majority either recovered (29.7%) or were recovering (45.5%). In contrast, hepatic failure and acute hepatic failure demonstrated a poor prognosis, with mortality rates of 44.2% and 32.9%, respectively. However, this is in line with the expected poor outcome in such conditions: in historical series, a mortality rate of approximately 80% has been described for acute hepatic failure [18].

Comparison of drug-related hepatic disorders caused by immune checkpoint inhibitors

The adverse drug reactions involving checkpoint inhibitors showed a mortality rate of 11.9%, which was similar to the overall death rate for hepatic adverse drug reactions. For all checkpoint inhibitors investigated, hepatitis was the most frequently reported drug reaction (nivolumab 24.7%; pembrolizumab 46.7%; ipilimumab 29.4%). Checkpoint inhibitors were associated with a remarkably higher occurrence of hepatitis and autoimmune hepatitis compared with all other suspected drugs. These results are in line with the known autoimmune side effects of checkpoint inhibitors: by inhibiting the suppressive effect of checkpoints on the immune system, they can lead to strongly enhanced immune reactions [9].

Compared with the other two checkpoint inhibitors, pembrolizumab was reported about twice as frequently to be associated with hepatitis. However, it was significantly less frequently reported to be related to autoimmune hepatitis than the other two substances. Hepatitis occurring as a side effect of checkpoint inhibitors is generally assumed to result from autoimmune mechanisms, and the significant differences in reporting of hepatitis and autoimmune hepatitis may be attributed to a reporting bias rather than to differing forms of hepatitis. A randomised clinical trial in advanced melanoma did not report the occurrence of hepatitis as a side effect for either nivolumab (n = 313) or for ipilimumab (n = 311). Only in the study group receiving nivolumab plus ipilimumab (n = 313) were seven cases of hepatitis documented [19]. Another randomised clinical trial compared ipilimumab with pembrolizumab in advanced melanoma. For ipilimumab, no hepatitis was reported. For pembrolizumab, only one event occurred within the observation period for the dosage regimen "every 2 weeks" whereas four events were documented for the dosage regimen "every 3 weeks" [20]. In a retrospective study that reviewed 496 patients with metastatic melanoma receiving nivolumab or pembrolizumab, 11 patients developed hepatitis of whom 2 had been treated with nivolumab and 9 with pembrolizumab [21]. Apart from the differences in the reporting of hepatitis and autoimmune hepatitis, no other significant discrepancies were found in the dispro-

portionality analysis, suggesting a similar safety profile of checkpoint inhibitors with regard to hepatic disorders. It has to be emphasised that disproportionality analyses allow only for exploratory approaches and for generating hypotheses. Exact risk quantification requires clinical trials where exposure is known and complete data are available. Clinical trials with a direct comparison regarding hepatic adverse events of the three substances are currently missing. However, a network meta-analysis has compared the checkpoint inhibitors: this study reported hepatic toxicities as predominant treatment-related adverse events only for pembrolizumab. For ipilimumab, skin, gastrointestinal and renal toxicities were mentioned as the main treatment-related adverse events, whereas for nivolumab, the network meta-analysis mainly reported endocrine toxicities [22].

Limitations and strengths

This study has major strengths. First, to the best of our knowledge, no other previous study has explored Swiss DILI cases in the WHO global pharmacovigilance database VigiBase™. Due to regional differences in prescribing and healthcare systems, or ethnical differences, drug-related hepatic disorders vary from country to country. A study using DILI registries from different countries found significant differences in the identified drugs causing DILI in the various regions [7]. Data from other countries may thus not necessarily be applicable to Switzerland. Second, analysis of a global pharmacovigilance database gives insights into real-world data and thus into events occurring in daily routine use. However, studies based on a spontaneous reporting system have some limitations. It needs to be emphasised that the VigiBase™ data are not appropriate for judging causality between a drug and a reaction. Only limited data can be extracted and investigated with this type of database. Thus, assessing a causal relationship is not possible since data regarding the temporal relationship, as well as information concerning de-/rechallenges, are missing. Moreover, information on possible comorbidity or other factors affecting hepatic function (e.g., alcohol consumption) is frequently not available. Underreporting or selective reporting is a further limitation of the spontaneous reporting system: increased reporting does not necessarily imply that a drug is really causing a certain adverse drug reaction more frequently. Reporting may be biased, for instance, by media reports or by authority warnings. Furthermore, data are missing in many ICSRs. Thus, the results need cautious interpretation owing to the limited information available. In our study, information regarding the indication/administration of drugs and “actions taken” was especially sparse. Another constraint of pharmacovigilance databases is the risk of duplicates. However, the algorithm vigiMatch, as well as the manual search for duplicates, allowed us to eliminate as many duplicates as possible. Another limitation is the heterogeneous documentation quality of the submitted reports. Therefore, this study focused on Swiss reports only, ensuring a homogeneous data quality.

Conclusion

Our findings highlight the importance of healthcare providers paying special attention to drug-induced liver injury, since these reactions resulted in a high mortality rate in this study. Also, special caution should be exercised regarding the substances paracetamol, amoxicillin/clavulanic acid, esomeprazole and atorvastatin, which ranked among the drugs most frequently suspected regarding severe drug-related hepatic disorders. However, Vigibase™ data are not appropriate for judging causality and thus these results should be interpreted with caution due to the possible influence of other comedication or comorbidity. The real-world pharmacovigilance data confirm the previous assumption for checkpoint inhibitors that hepatitis is the most frequent hepatic adverse event. Further studies are warranted to directly compare hepatic adverse drug events of different checkpoint inhibitors.

Financial disclosure

PP was funded by a scholarship for visiting scientists provided by the University of Zurich.

Potential competing interests

The authors declare no conflicts of interest in connection with the contents of this article. The Department of Clinical Pharmacology and Toxicology is a regional pharmacovigilance centre that reports to the national competent agency, Swissmedic. The data for this work were obtained from VigiLyze™, the software of the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. Data from spontaneous reporting are inhomogeneous as a result of different reporting policies worldwide and are subject to underreporting and reporting bias. The information contained in this work is therefore not homogeneous, at least with respect to origin and also to the likelihood that the pharmaceutical product caused the adverse reaction. The conclusions drawn based on these data do not necessarily represent the opinion of the World Health Organization.

References

1 Lee WM. Drug-induced acute liver failure. Clin Liver Dis. 2013;17(4):575–86, viii. doi: http://dx.doi.org/10.1016/j.cld.2013.07.001. PubMed.

2 Larrey DPageaux GP. Drug-induced acute liver failure. Eur J Gastroenterol Hepatol. 2005;17(2):141–3. doi: http://dx.doi.org/10.1097/00042737-200502000-00002. PubMed.

3 Fontana RJHayashi PHGu JReddy KRBarnhart HWatkins PBDILIN Network. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroenterology. 2014;147(1):96–108.e4. doi: http://dx.doi.org/10.1053/j.gastro.2014.03.045. PubMed.

4 Kullak-Ublick GAAndrade RJMerz MEnd PBenesic AGerbes AL Drug-induced liver injury: recent advances in diagnosis and risk assessment. Gut. 2017;66(6):1154–64. doi: http://dx.doi.org/10.1136/gutjnl-2016-313369. PubMed.

5 Hoofnagle JHBjörnsson ES. Drug-Induced Liver Injury - Types and Phenotypes. N Engl J Med. 2019;381(3):264–73. doi: http://dx.doi.org/10.1056/NEJMra1816149. PubMed.

6 Ferrajolo CCapuano AVerhamme KMSchuemie MRossi FStricker BH Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol. 2010;70(5):721–8. doi: http://dx.doi.org/10.1111/j.1365-2125.2010.03754.x. PubMed.

7 Suzuki AAndrade RJBjornsson ELucena MILee WMYuen NA Drugs associated with hepatotoxicity and their reporting frequency of liver adverse events in VigiBase: unified list based on international collaborative work. Drug Saf. 2010;33(6):503–22. doi: http://dx.doi.org/10.2165/11535340-000000000-00000. PubMed.

8 Liakoni ERätz Bravo AEKrähenbühl S. Hepatotoxicity of New Oral Anticoagulants (NOACs). Drug Saf. 2015;38(8):711–20. doi: http://dx.doi.org/10.1007/s40264-015-0317-5. PubMed.

9 Postow MASidlow RHellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158–68. doi: http://dx.doi.org/10.1056/NEJMra1703481. PubMed.

10 VigiBase [cited 2020 Nov 24]. Available from: https://www.who-umc.org/.

11 Standardised MedDRA Queries (SMQs) [cited 2020 Nov 24]. Available from: https://www.meddra.org.

12 Rothman KJLanes SSacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug

Saf. 2004;13(8):519–23. doi: http://dx.doi.org/10.1002/pds.1001. PubMed.

13 Chalasani NFontana RJBonkovsky HLWatkins PBDavern TSerrano JDrug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135(6):1924–34, 1934.e1–4. doi: http://dx.doi.org/10.1053/j.gastro.2008.09.011. PubMed.

14 Suzuki AYuen NAIlic KMiller RTReese MJBrown HR Comedications alter drug-induced liver injury reporting frequency: Data mining in the WHO VigiBase™. Regul Toxicol Pharmacol. 2015;72(3):481–90. doi: http://dx.doi.org/10.1016/j.yrtph.2015.05.004. PubMed.

15 Swiss drug information [cited 2020 Nov 27]. Available from: https://www.swissmedicinfo.ch.

16 LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012- [cited 2020 Nov 30]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/.

17 Helsana Arzneimittel-Report Ausgabe. 2020 [cited 2021 Jan 26]. Available from: https:// www.helsana.ch.

18 Rovegno MVera MRuiz ABenítez C. Current concepts in acute liver failure. Ann Hepatol. 2019;18(4):543–52. doi: http://dx.doi.org/10.1016/j.aohep.2019.04.008. PubMed.

19 Wolchok JDChiarion-Sileni VGonzalez RRutkowski PGrob JJCowey CL Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017;377(14):1345–56. doi: http://dx.doi.org/10.1056/NEJMoa1709684. PubMed.

20 Schachter JRibas ALong GVArance AGrob JJMortier L Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet. 2017;390(10105):1853–62. doi: http://dx.doi.org/10.1016/S0140-6736(17)31601-X. PubMed.

21 Hofmann LForschner ALoquai CGoldinger SMZimmer LUgurel S Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer. 2016;60:190–209. doi: http://dx.doi.org/10.1016/j.ejca.2016.02.025. PubMed.

22 Xu CChen YPDu XJLiu JQHuang CLChen L Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 2018;363:k4226. doi: http://dx.doi.org/10.1136/bmj.k4226. PubMed.

Appendix

Supplementary tables

Table S1: Most frequent drugs (accounting for at least 1% of drugs) of all those reported (regardless of causality).

All reported drugs	ATC code	Frequency	Percent of all drugs	Percent of patients
Paracetamol	N02BE01	391	3.7	19.1
Acetylsalicylic acid	N02BA01	244	2.3	11.9
Pantoprazole	A02BC02	225	2.2	11.0
Esomeprazole	A02BC05	195	1.9	9.5
Torasemide	C03CA04	169	1.6	8.3
Atorvastatin	C10AA05	162	1.5	7.9
Amoxicillin / clavulanic acid	J01CR02	152	1.5	7.4
Metoprolol	C07AB02	145	1.4	7.1
Prednisone	H02AB07	124	1.2	6.1
Metamizole	N02BB02	120	1.1	5.9
Amlodipine	C08CA01	104	1.0	5.1
Calcium carbonate / cholecalciferol	A12AX	103	1.0	5.0
Others		8330	79.6	
ATC = Anatomical Therapeutic Chemical				

Table S2: Outcomes of the most frequent adverse drug reactions.

Reaction (% per reaction)	Frequency outcome (% per reaction)							
	Missing	Died	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown	Total
Acute hepatic failure	1 (1.2%)	27 (32.9%)	5 (6.1%)	23 (28.0%)	2 (2.4%)	18 (22.0%)	6 (7.3%)	82
Acute kidney injury	0 (0.0%)	21 (25.0%)	6 (7.1%)	30 (35.7%)	2 (2.4%)	18 (21.4%)	7 (8.3%)	84
Ascites	0 (0.0%)	11 (11.1%)	12 (12.1%)	19 (19.2%)	1 (1.0%)	10 (10.1%)	46 (46.5%)	99
Cholestatic liver injury	1 (0.4%)	4 (1.6%)	67 (26.0%)	73 (28.3%)	1 (0.4%)	91 (35.3%)	21 (8.1%)	258
Diarrhoea	0 (0.0%)	2 (3.1%)	8 (12.5%)	27 (42.2%)	1 (1.6%)	3 (4.7%)	23 (35.9%)	64
Drug-induced liver injury	0 (0.0%)	4 (2.4%)	14 (8.5%)	49 (29.7%)	0 (0.0%)	75 (45.5%)	23 (13.9%)	165
Fatigue	1 (1.5%)	1 (1.5%)	13 (19.4%)	17 (25.4%)	0 (0.0%)	8 (11.9%)	27 (40.3%)	67
Hepatic enzyme increased	0 (0.0%)	6 (7.7%)	8 (10.3%)	17 (21.8%)	0 (0.0%)	32 (41.0%)	15 (19.2%)	78
Hepatic failure	3 (2.9%)	46 (44.2%)	8 (7.7%)	17 (16.3%)	0 (0.0%)	12 (11.5%)	18 (17.3%)	104
Hepatitis	0 (0.0%)	3 (1.7%)	23 (12.8%)	46 (25.7%9	0 (0.0%)	53 (29.6%)	54 (30.2%)	179
Hepatitis cholestatic	0 (0.0%)	5 (6.2%)	11 (13.6%)	25 (30.9%)	0 (0.0%)	33 (40.7%)	7 (8.6%)	81
Hepatocellular carcinoma	0 (0.0%)	12 (18.2%)	10 (15.2%)	2 (3.0%)	0 (0.0%)	2 (3.0%)	40 (60.6%)	66
Hepatocellular injury	1 (0.3%)	12 (4.1%)	26 (8.8%)	95 (32.3%)	3 (1.0%)	130 (44.2%)	27 (9.2%)	294
Hepatotoxicity	0 (0.0%)	2 (3.0%)	8 (12.1%)	20 (30.3%)	0 (0.0%)	9 (13.6%)	27 (40.9%)	66
Jaundice	1 (0.5%)	15 (8.0%)	36 (19.3%)	63 (33.7%)	2 (1.1%)	42 (22.5%)	28 (15.0%)	187
Liver disorder	0 (0.0%)	5 (3.9%)	15 (11.8%)	26 (20.5%)	1 (0.8%)	31 (24.4%)	49 (38.6%)	127
Liver injury	0 (0.0%)	9 (4.3%)	19 (9.1%)	82 (39.4%)	2 (1.0%)	68 (32.7%)	28 (13.5%)	208
Mixed liver injury	0 (0.0%)	1 (0.7%)	23 (16.1%)	48 (33.6%)	0 (0.0%)	61 (42.7%)	10 (7.0%)	143
Nausea	1 (1.1%)	4 (4.2%)	4 (4.2%)	48 (50.5%)	0 (0.0%)	17 (17.9%)	21 (22.1%)	95
Pruritus	1 (1.6%)	0 (0.0%)	15 (23.8%)	19 (30.2%)	0 (0.0%)	11 (17.5%)	17 (27.0%)	63
Pyrexia	4 (4.4%)	1 (1.1%)	6 (6.6%)	63 (69.2%)	0 (0.0%)	7 (7.7%)	10 (11.0%)	91
Vomiting	0 (0.0%)	5 (8.1%)	1 (1.6%)	34 (54.8%)	1 (1.6%)	6 (9.7%)	15 (24.2%)	62