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RESEARCH ARTICLE

Drug-induced liver injury associated with lopinavir-ritonavir in patients with COVID-19: a disproportionality analysis of U.S. food and drug administration adverse event reporting system (FAERS) data

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Abstract

Background Liver injury has been documented independently in novel coronavirus disease 2019 (COVID-19) patients and patients treated with lopinavir-ritonavir. *Objective* to investigate the drug-induced liver injury associated with lopinavir-ritonavir among the patients with COVID-19. *Methods* We conducted a disproportionality analysis of US Food and Drug Administration Adverse Event Reporting System (FAERS) between 2020Q1 and 2021Q1 to evaluate the association between lopinavir-ritonavir and risk of drug-induced liver injury (or severe drug-induced liver injury) and calculated their reporting odds ratios (RORs) with 95% confidence intervals (CIs). *Results* A total of 3,425 cases of drug-induced liver injury were reported in 19,782 patients with COVID-19. The ROR for drug-induced liver injury was 2.99 (2.59–3.46), 3.16 (2.68–3.73), and 5.39 (4.63–6.26) when comparing lopinavir-ritonavir with all other drugs, hydroxychloroquine/chloroquine only, and remdesivir, respectively. For severe drug-induced liver injury, RORs for lopinavir-ritonavir provided evidence of an association compared with all other drugs (3.98; 3.15–5.05), compared with hydroxychloroquine/chloroquine only (5.33; 4.09–6.94), and compared with remdesivir (3.85; 3.03–4.89). *Conclusions* In the FAERS, we observed a disproportional signal for drug-induced liver injury associated with lopinavir-ritonavir in patients with COVID-19.

Keywords FAERS · Liver injury · Lopinavir-ritonavir · Novel coronavirus disease 2019

Impacts on practice

- COVID-19 patients treated with lopinavir-ritonavir are at increased risk of liver injury.

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- The risk of liver injury reinforces recent guidelines recommending against the use of lopinavir-ritonavir in COVID-19.
- Further study of lopinavir-ritonavir is required to better characterize the risk factors and outcomes of liver injury in treated patients.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has become a global public health crisis. COVID-19 not only produces clusters of severe respiratory illness but also leads to multiorgan failure and death [1]. Liver injury is common in patients with COVID-19 and is more commonly observed in severe COVID-19 [2]. The mechanism by which COVID-19 may lead to elevated liver enzymes is unclear, but it may be related to several factors including direct virus-induced cytopathic effect, thromboembolic complications, and COVID-19-associated cytokine release [2]. Drug-induced liver injury is another important potential contributor [3], but data are limited regarding drug hepatoxicity in patients with COVID-19.

Lopinavir-ritonavir, a fixed-dose combination antiretroviral drug widely used for the treatment and prevention of HIV/AIDS, has also been a potential candidate for treating COVID-19 in the early pandemic [4]. Moreover, lopinavir-ritonavir is considered as an independent factor for liver injury [5]; however, liver injury associated with lopinavir-ritonavir in COVID-19 patients has not been well described.

Aim of the study

In this study, we investigated the drug-induced liver injury associated with lopinavir-ritonavir from the US Food and Drug Administration Adverse Event Reporting System (FAERS).

Ethics approval

The study requires no ethics approval.

Methods

FAERS, a publicly available spontaneous reporting system, is designed to support the FDA's post-marketing surveillance for drug and therapeutic biologic products. The FAERS containing drug AE reports, product quality complaints, and medication error reports, is published every quarter. As of March 31 (Q1), 2021 (the most recent update date at submission), a total of 22,002,078 adverse event reports were submitted to FAERS.

In this study, we extracted data for patients with COVID-19 from FAERS between January 1, 2020 (2020 Q1) and 2021 Q1 using the COVID-19 related terms within Medical Dictionary for Regulatory Activities (MedDRA, version 23.1) (See Table 1). Our outcomes included drug-induced liver injury and severe drug-induced liver injury, which were identified by a narrow Standardized MedDRA Query (SMQ) of "drug related hepatic disorders" and by a narrow SMQ of "drug related hepatic disorders—severe events only", respectively (definitions shown in Table 1) [6]. All drugs of interest were identified through their generic and brand names.

We conducted a disproportionality analysis and calculated reporting odds ratios (RORs) with 95% confidence intervals (CI) [7] for the following comparisons: (1) lopinavir-ritonavir versus all other drugs (all drugs except lopinavir-ritonavir used in the COVID-19 cases); (2) lopinavir-ritonavir versus hydroxychloroquine/chloroquine; (3) lopinavir-ritonavir versus remdesivir. The ROR is calculated by dividing the odds of a liver injury event reported for the drug of interest by the odds of a liver injury event reported for the comparison drugs. Additionally, we performed stratified analyses by age (<65 years vs. $>=65$ years), sex (female vs. male), and country where the reports were created (within the United States vs. outside of the United States). We defined a signal of increased risk using a ROR ≥ 2 with a chi-squared test statistic ≥ 4 [8]. Data analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 19,782 patients with COVID-19 (845 for lopinavir-ritonavir and 18,937 for all other drugs combined) were identified within FAERS from 2020 Q1 to 2021 Q1. Of those, 3425 were reported to have a drug-induced liver injury. The flowchart of the identification of drug-induced liver injury in patients with COVID-19 was presented in Fig. 1. The basic characteristics of COVID-19 cases were reported in Table 1.

For lopinavir-ritonavir, 313/845 (37.0%) of reported adverse events were for drug-induced liver injury, compared to 3,112/18,937 (16.4%) for all other drugs combined. The ROR for drug-induced liver injury was 2.99 (95% CI, 2.59–3.46) when comparing lopinavir-ritonavir with all other drugs (Table 2). When lopinavir-ritonavir was compared with hydroxychloroquine/chloroquine only and remdesivir, the ROR for drug-induced liver injury was 3.16 (95% CI, 2.68–3.73) and 5.39 (95% CI, 4.63–6.26), respectively (Table 2). For severe drug-induced liver injury, RORs for lopinavir-ritonavir provided evidence of an association compared with all other drugs (ROR, 3.98; 95% CI, 3.15–5.05), compared with hydroxychloroquine/chloroquine (ROR,

Table 1 Descriptive characteristics of COVID-19 cases[a] reported to FAERS from January 1st (Q1), 2020 to March 31st (Q1), 2021

Characteristic	Lopinavir-ritonavir ($n=845$)	All other drugs[b] ($n=18,937$)
Age, years ($n=$)		
Mean ± SD	63.09 ± 14.79	59.23 ± 19.95
> = 65 years, $n=$	395	7295
< 65 years, $n=$	393	8,559
Sex, $n=$		
Female	233	6879
Male	555	10,111
Country, $n=$		
Within the united states	19	11,496
Outside of the united states	826	7441
Concurrent drugs, $n=$		
Hydroxychloroquine/chloroquine	225	4017
Remdesivir	7	5142
ADEs of interest, $n=$		
Drug-induced liver injury[c]	313	3112
Severe drug-induced liver injury[d]	90	672

ADE adverse events, *SD* standard deviation, *FAERS* food and drug administration adverse event reporting system

[a]MedDRA preferred terms related to COVID-19 including "asymptomatic COVID-19", "COVID-19", "COVID-19 pneumonia", "suspected COVID-19", "SARS-COV-2 carrier", "exposure to SARS-COV-2", "occupational exposure to communicable disease", "occupational exposure to SARS-COV-2", "coronavirus test", "coronavirus test negative", "SARS-COV-2 test", "SARS-COV-2 test false negative", "SARS-COV-2 test negative", "SARS-COV-2 test positive", "COVID-19 prophylaxis", "COVID-19 treatment", "COVID-19 immunisation", "patient isolation", "quarantine", "multisystem inflammatory syndrome in children", "SARS-COV-2 sepsis", "SARS-COV-2 viraemia", "SARS-COV-2 test false positive", "SARS-COV-2 antibody test"

[b]All other drugs including the all drugs except lopinavir-ritonavir used in the COVID-19 cases

[c]Identified by a narrow SMQ of "Drug related hepatic disorders," which includes narrow scope of cholestasis and jaundice of hepatic origin, liver related investigations, signs and symptoms, liver-related coagulation and bleeding disturbances, noninfectious hepatitis, hepatic failure, fibrosis, cirrhosis, other drug-related liver damage, liver neoplasms (benign, including cysts and polyps), and liver neoplasms (malignant and unspecified)

[d]Identified by a narrow SMQ of "Drug related hepatic disorders—severe events only," which includes narrow scope of noninfectious hepatitis, hepatic failure, fibrosis, cirrhosis, other drug-related liver damage, liver neoplasms (benign, including cysts and polyps), and liver neoplasms (malignant and unspecified)

5.33; 95% CI, 4.09–6.94), and compared with remdesivir (ROR, 3.85; 95% CI, 3.03–4.89) (Table 2).

When conducting further analyses stratified by age (< 65 years vs. > = 65 years), sex (female vs. male), and country where the reports were created (within the United States outside of the United States), we also detected a signal of increased risk of both drug-induced liver injury and severe drug-induced liver injury associated with lopinavir-ritonavir in patients with COVID-19 (Table 3).

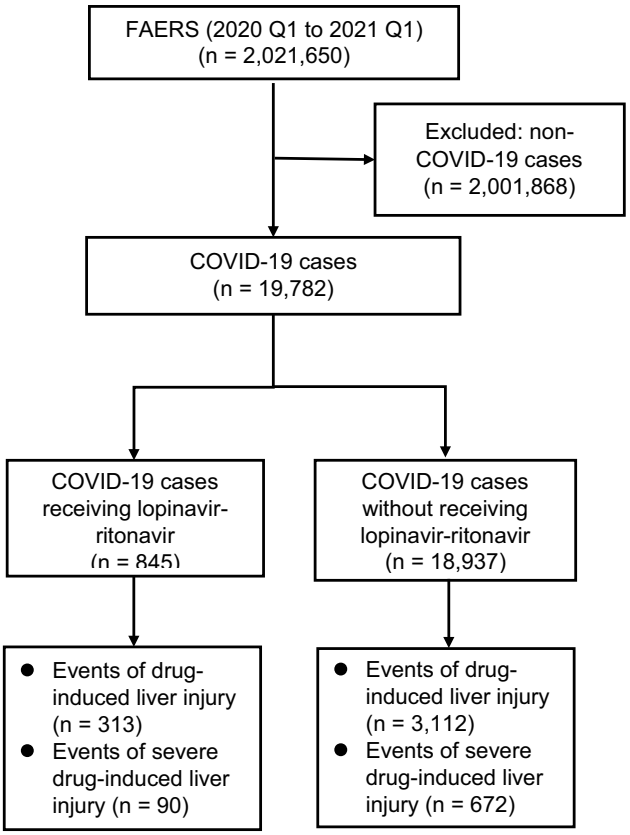

Fig.1 Flowchart of the identification of drug-induced liver injury in patients with COVID-19 from US food and drug administration adverse event reporting system (FAERS) between January 1 (Q1), 2020 and March 31 (Q1), 2021

Discussion

In this disproportionality analysis of FAERS data, we detected signals of increased risks of both drug-induced liver injury and severe drug-induced liver injury associated with lopinavir-ritonavir versus all other drugs, hydroxychloroquine/chloroquine, and remdesivir in patients with COVID-19. The results from the further stratified analyses supported our findings.

Lopinavir-ritonavir has been reported to be associated with moderate-to-severe elevations in serum aminotransferase levels in prior studies [3, 9], which supported our finding that lopinavir-ritonavir might be associated with an increased risk of drug-induced liver injury. Additionally, our results were consistent with the evidence from recent studies [10, 11]. One retrospective case series in China showed that

Table 2 Reporting odds ratio for the lopinavir-ritonavir compared to other drugs in patients with COVID-19[a]

Comparison	No. of liver injury/No. of other ADEs		Reporting odds ratio (95% CI)	Chi-squared test statistic (*p*-value)
	Lopinavir-ritonavir	Comparator		
Drug-induced liver injury[c]				
Lopinavir-ritonavir vs all other drugs[b]	313/532	532/15,825	2.99 (2.59–3.46)	240.00 (<0.0001)
Lopinavir-ritonavir vs hydroxychloroquine/chloroquine	249/371	2,614/3,404	3.16 (2.68, 3.73)	203.04 (<0.0001)
Lopinavir-ritonavir vs remdesivir	311/527	1,362/12,433	5.39 (4.63, 6.26)	578.87 (<0.0001)
Severe drug-induced liver injury [d]				
Lopinavir-ritonavir vs all other drugs	90/532	672/15,825	3.98 (3.15, 5.05)	152.32 (<0.0001)
Lopinavir-ritonavir vs hydroxychloroquine/chloroquine	75/371	467/12,306	5.33 (4.09, 6.94)	189.81 (<0.0001)
Lopinavir-ritonavir vs remdesivir	90/367	552/12,433	3.85 (3.03, 4.89)	139.92 (<0.0001)

ADEs adverse drug events, *SMQ* standardized medical dictionary for regulatory activities query

[a]MedDRA preferred terms related to COVID-19 including "asymptomatic COVID-19", "COVID-19", "COVID-19 pneumonia", "suspected COVID-19", "SARS-COV-2 carrier", "exposure to SARS-COV-2", "occupational exposure to communicable disease", "occupational exposure to SARS-COV-2", "coronavirus test", "coronavirus test negative", "SARS-COV-2 test", "SARS-COV-2 test false negative", "SARS-COV-2 test negative", "SARS-COV-2 test positive", "COVID-19 prophylaxis", "COVID-19 treatment", "COVID-19 immunisation", "patient isolation", "quarantine", "multisystem inflammatory syndrome in children", "SARS-COV-2 sepsis", "SARS-COV-2 viraemia", "SARS-COV-2 test false positive", "SARS-COV-2 antibody test"

[b]All other drugs including the all drugs except lopinavir-ritonavir used in the COVID-19 cases

[c]Identified by a narrow SMQ of "Drug related hepatic disorders," which includes narrow scope of cholestasis and jaundice of hepatic origin, liver related investigations, signs and symptoms, liver-related coagulation and bleeding disturbances, noninfectious hepatitis, hepatic failure, fibrosis, cirrhosis, other drug-related liver damage, liver neoplasms (benign, including cysts and polyps), and liver neoplasms (malignant and unspecified)

[d]Identified by a narrow SMQ of "Drug related hepatic disorders—severe events only," which includes narrow scope of noninfectious hepatitis, hepatic failure, fibrosis, cirrhosis, other drug-related liver damage, liver neoplasms (benign, including cysts and polyps), and liver neoplasms (malignant and unspecified)

a higher proportion of patients with abnormal liver function had taken lopinavir-ritonavir after admission than those with normal liver function (57.8% vs. 31.3%) [11]. Another case series of 417 patients with COVID-19 also found that the use of lopinavir/ritonavir was associated with increased odds of liver injury (OR from 4.44 to 5.03, both $p < 0.01$).[10] The mechanism of lopinavir-ritonavir induced hepatotoxicity may be due to its metabolism by the cytochrome P450 (CYP) system (primarily CYP3A4) in the liver[12]. Physicians should be aware of the potential risks, including liver injury especially when combining lopinavir-ritonavir with the drugs metabolized by CYP450 enzyme (e.g., chloroquine and hydroxychloroquine) [13].

Moreover, it should be noted that the role of lopinavir-ritonavir in the treatment and preventing of COVID-19 has changed over time. In the early pandemic, lopinavir-ritonavir was considered to be a potential treatment for COVID-19, but then the following trials found that the use of lopinavir-ritonavir did not significantly enhance clinical improvement in adults hospitalized with severe COVID-19 [5, 14]. Accordingly, the guidelines from WHO [15] and Infections Disease Society of America (IDSA) [16] recommended against treating with lopinavir-ritonavir in hospitalized patients with COVID-19. Hydroxychloroquine/chloroquine, another repurposed drug for treating COVID-19, has also been withdrawn the emergency use authorization to treat hospitalized patients with COVID-19 by the US FDA [17], and that use of the agent is not supported by WHO [15].

This study has limitations. Spontaneous events reporting is subject to reporting bias and the lack of denominators to estimate risks of adverse events. Given the limited information available in the FAERS database, we cannot control the confounders in our analysis, which include comorbidities, concomitant medications, or severity of COVID-19. Although disproportionality analysis is a useful tool for signal detection, causality regarding the association between lopinavir-ritonavir and drug-induced liver injury cannot be established by this study, and further research is needed to supplement our findings.

Conclusion

In conclusion, we observed a disproportional signal for drug-induced liver injury associated with lopinavir-ritonavir in patients with COVID-19, indicating that patients treated with lopinavir-ritonavir may be at increased risk of liver injury. Given little evidence of the benefit of the use of lopinavir-ritonavir in patients with COVID-19, WHO has recommended against the use of lopinavir-ritonavir in hospitalized patients with COVID-19. Further studies that evaluate the role of lopinavir-ritonavir in patients with COVID-19 are not

Table 3 Stratified analysis of the reporting odds ratio for the lopinavir-ritonavir compared to other drugs in COVID-19 cases[a]

Comparison	No. of liver injury/No. of other ADEs		Reporting odds ratio (95% CI)	Chi-squared test statistic (*p*-value)
	Lopinavir-ritonavir	Comparator		
Drug-induced liver injury[c]				
Lopinavir-ritonavir vs all other drugs[b]				
Age < 65 years	177/216	1,687/6,872	3.34 (2.72, 4.10)	146.20 (< 0.0001)
Age > = 65 years	125/260	1,050/6,230	2.85 (2.28, 3.57)	91.73 (< 0.0001)
Male	223/332	1,891/8,220	2.91 (2.44, 3.48)	152.72 (< 0.0001)
Female	79/154	889/5,990	3.46 (2.61–4.57)	84.38 (< 0.0001)
Within the United States	5/14	1,831/9,679	1.89 (0.68, 5.24)	1.53 (0.22)
Outside of the United States	308/518	1,281/6,160	2.86 (2.45, 3.33)	192.93 (< 0.0001)
Lopinavir-ritonavir vs hydroxychloroquine/chloroquine				
Age < 65 years	146/141	1,414/5,099	3.73 (2.94, 4.74)	132.22 (< 0.0001)
Age > = 65 years	99/194	936/5,086	2.77 (2.16, 3.57)	67.88 (< 0.0001)
Male	175/239	1,629/6,356	2.86 (2.33, 3.50)	111.62 (< 0.0001)
Female	70/100	765/4,874	4.46 (3.26, 6.11)	102.19 (< 0.0001)
Within the United States	3/9	1,718/8,643	1.68 (0.45,6.20)	0.61 (0.43)
Outside of the United States	246/362	896/3,663	2.78 (2.33, 3.32)	134.90 (< 0.0001)
Lopinavir-ritonavir vs remdesivir				
Age < 65 years	176/213	681/5,468	6.63 (5.35, 8.23)	8.06 (0.0045)
Age > = 65 years	124/259	368/4,534	5.90 (4.64, 7.49)	260.23 (< 0.0001)
Male	222/329	736/6,327	5.80 (4.81, 6.99)	414.61 (< 0.0001)
Female	78/152	323/4590	7.29 (5.42, 9.80)	228.42 (< 0.0001)
Within the united states	3/11	294/6,814	6.32 (1.75, 22.78)	10.46 (0.0012)
Outside of the united states	308/516	1,068/5,619	3.14 (2.69, 3.67)	224.67 (< 0.0001)
Severe drug-induced liver injury[d]				
Lopinavir-ritonavir vs all other drugs				
Age < 65 years	72/216	399/6,872	5.74 (4.32, 7.64)	180.52 (< 0.0001)
Age > = 65 years	15/260	166/6,230	2.17 (1.26, 3.73)	8.17 (0.0043)
Male	66/332	431/8,220	3.79 (2.86, 5.02)	98.65 (< 0.0001)
Female	21/154	144/5,990	5.67 (3.49, 9.21)	62.24 (< 0.0001)
Within the united states	0/14	106/9,665	NA	NA
Outside of the united states	90/518	566/6,160	1.89 (1.49, 2.40)	27.93(< 0.0001)
Lopinavir-ritonavir vs hydroxychloroquine/chloroquine				
Age < 65 years	61/141	262/5099	8.42 (6.08, 11.65)	228.03(< 0.0001)
Age > = 65 years	13/194	128/5086	2.66 (1.48, 4.80)	11.50 (0.0007)
Male	56/239	298/6356	5.00 (3.65, 6.84)	122.92(< 0.0001)
Female	18/100	102/4874	8.60 (5.02, 14.74)	87.37 (< 0.0001)
Within the united states	0/9	101/8643	NA	NA
Outside of the united states	75/362	366/3663	2.07 (1.58, 2.72)	28.91 (< 0.0001)
Lopinavir-ritonavir vs remdesivir				
Age < 65 years	72/213	337/5468	5.48 (4.11, 7.32)	164.17 (< 0.0001)
Age > = 65 years	15/259	124/4534	2.12 (1.22, 3.67)	7.47 (0.0063)
Male	66/329	359/6327	3.54 (2.66, 4.70)	85.00 (< 0.0001)
Female	21/152	107/4590	5.93 (3.61, 9.72)	63.39 (< 0.0001)
Within the united states	0/11	34/6814	NA	NA
Outside of the united states	90/516	518/5619	1.89 (1.49, 2.41)	27.63 (< 0.0001)

ADEs adverse drug events, *SMQ* standardized medical dictionary for regulatory activities query, *NA* not applicable

[a]MedDRA preferred terms related to COVID-19 including "asymptomatic COVID-19", "COVID-19", "COVID-19 pneumonia", "suspected COVID-19", "SARS-COV-2 carrier", "exposure to SARS-COV-2", "occupational exposure to communicable disease", "occupational exposure to SARS-COV-2", "coronavirus test", "coronavirus test negative", "SARS-COV-2 test", "SARS-COV-2 test false negative", "SARS-COV-2 test negative", "SARS-COV-2 test positive", "COVID-19 prophylaxis", "COVID-19 treatment", "COVID-19 immunisation", "patient isolation", "quarantine", "multisystem inflammatory syndrome in children", "SARS-COV-2 sepsis", "SARS-COV-2 viraemia", "SARS-COV-2 test false

Table 3 (continued)

positive", "SARS-COV-2 antibody test"

[b]all other drugs including the all drugs except lopinavir-ritonavir used in the COVID-19 cases

[c]identified by a narrow SMQ of "Drug related hepatic disorders," which includes narrow scope of cholestasis and jaundice of hepatic origin, liver related investigations, signs and symptoms, liver-related coagulation and bleeding disturbances, noninfectious hepatitis, hepatic failure, fibrosis, cirrhosis, other drug-related liver damage, liver neoplasms (benign, including cysts and polyps), and liver neoplasms (malignant and unspecified)

[d] identified by a narrow SMQ of "Drug related hepatic disorders—severe events only," which includes narrow scope of noninfectious hepatitis, hepatic failure, fibrosis, cirrhosis, other drug-related liver damage, liver neoplasms (benign, including cysts and polyps), and liver neoplasms (malignant and unspecified)

warranted and need prior careful ethical consideration. The risks of the over-zealous use of repurposed drugs to treat patients with COVID-19 should be carefully considered.

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Declarations

Conflicts of interest HT is a consultant for Evidpro, LLC. The other authors have no conflict of interest to declare.

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