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Article

Analysis of reported adverse liver reactions associated with drugs used to treat patients with coronavirus disease 2019

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Hepatic injury has been documented in patients with coronavirus disease 2019 (COVID-19). However, pharmacotherapy can frequently impact liver alterations, given the known hepatotoxic potential of drugs not effective to treat COVID-19. The objective of the present study was to evaluate reports of suspected liver reactions to drugs used for treating COVID-19, compare their use for other indications among patients with COVID-19, and assess possible interactions between them. We obtained reports on drugs used to treat COVID-19 (tocilizumab, remdesivir, hydroxychloroquine, and/or lopinavir/ritonavir), registered on June 30, 2020, from the Food and Drug Administration Adverse Event Reporting System (FAERS) Public Dashboard. We then analyzed the risk of developing liver events with these drugs by calculating the reported odds ratios (ROR). We identified 662, 744, and 1381 reports related to tocilizumab, lopinavir/ritonavir, and hydroxychloroquine use, respectively. The RORs (95% confidence intervals) were 6.32 (5.28–7.56), 6.12 (5.22–7.17), and 9.07 (8.00–10.29), respectively, demonstrating an increased risk of liver events among patients with COVID-19 when compared with uninfected patients. The elevated risk of reporting adverse liver events in patients with COVID-19 who receive these drugs, alone or in combination, highlights the need for careful drug selection and efforts to reduce drug combinations without notable benefits. Similar to any other condition, the use of drugs without established efficacy should be avoided.

Keywords: COVID-19. Hepatotoxicity. Pharmacovigilance. Drug-drug interaction.

INTRODUCTION

In March 2020, the World Health Organization declared the coronavirus disease (COVID-19) pandemic, and more than 100 million infections and 2 million deaths were reported in the first year of the pandemic (Carvalho, Krammer, Iwasaki, 2021). COVID-19 is a complex disease affecting multiple organs, including the liver and kidneys (Gulati *et al.*, 2020). As a well-known complication, liver injury (such as increased liver enzymes) has been documented in both intensive care unit (ICU) and non-ICU patients. The underlying cause of liver dysfunction in patients with COVID-19 is multifactorial and may be related to direct virus-induced cytopathic damage to bile duct cells, coupled with serious inflammation and/or drug-induced liver injury (Zhao *et al.*, 2020; Li, Fan, 2020; Xu *et al.*, 2020; Yadav *et al.*, 2021; Marjot *et al.*, 2021).

Although an effective etiological treatment for COVID-19 is yet to be established, thousands of clinical trials and observational studies assessing at least 25 candidate treatments have been conducted. These experimental treatments include antivirals, antimalarials, and monoclonal antibodies such as tocilizumab, remdesivir, hydroxychloroquine, and/or lopinavir/ritonavir (L/r) (McCarthy *et al.*, 2020; Siemieniuk *et al.*, 2020).

However, recent studies have found that hydroxychloroquine, L/r, and remdesivir fail to reduce mortality, the need for mechanical ventilation, or the duration of hospitalization. Conversely, tocilizumab

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could reduce the risk of mechanical ventilation and ICU admission but fails to reduce mortality (Pan *et al.*, 2020; Lin *et al.*, 2021).

Hydroxychloroquine and other off-label drugs without proven therapeutic efficacy against COVID-19 have been persistently used in Brazil (Santos-Pinto, Miranda, Osorio-de-Castro, 2021) and the USA (Bull-Otterson *et al.*, 2020). Exposure to these agents can increase the risk of unexpected adverse drug reactions or potentiate known effects, such as hepatotoxicity. A review of published studies and official documents has observed that remdesivir was associated with transient treatment-emergent elevations in aminotransferases, documented in clinical (Wang *et al.*, 2020; Grein *et al.*, 2020; European Medicines Agency, 2020) and observational studies (Lescure *et al.*, 2020; Kujawski *et al.*, 2020), including cases of premature treatment discontinuation (Grein *et al.*, 2020; European Medicines Agency, 2020). An analysis of VigiBase, the World Health Organization's Individual Case Safety Reports database, found 130 (34%) reported adverse hepatic effects among 387 reports of remdesivir use (Montastruc, Thuriot, Durrieu, 2020). The authors concluded that the risk of reporting hepatic disorders was greater with remdesivir than that with other treatments, including tocilizumab, used to manage severe COVID-19 (Montastruc, Thuriot, Durrieu, 2020).

Elevated serum aminotransferase levels have been documented in a high proportion of patients treated with L/r-containing antiretroviral regimens, primarily in those with human immunodeficiency virus and hepatitis C virus coinfections, although clinically relevant liver injury remains rare. In clinical trials, the use of L/r combined with other antiretrovirals has been associated with an incidence of hepatotoxicity ranging from 1–9.5% (Sulkowski, 2004). In 2019, Canada and New Zealand published warnings regarding the risk of hepatotoxicity associated with tocilizumab (Health Canada, 2019; Campbell, 2019). Hydroxychloroquine, a known antimalarial and anti-rheumatologic agent, has not been associated with a significant risk of hepatotoxic events, but clinically apparent liver injury has been described in some case reports (LiverTox, 2012; Falcão *et al.,* 2020; Abdel, 2015).

Therefore, the present study was designed to evaluate the occurrence of disproportionality in the chance of reporting liver events and hepatitis, comparing the use of tocilizumab, remdesivir, hydroxychloroquine, and/or L/r used to treat COVID-19 with other applications of these therapeutics, based on reports included in the Food and Drug Administration Adverse Event Reporting System (FAERS) pharmacovigilance database. In addition, the possible interactions between these agents were analyzed

METHODS

Study design and population

In this cross-sectional study, we used the FAERS Public Dashboard as the data source. The study population comprised patients who presented suspected adverse drug reactions (ADRs) associated with drugs used to treat COVID-19 (tocilizumab, remdesivir, hydroxychloroquine and/or L/r) and were notified to FAERS by June 30, 2020.

In the FAERS Public Dashboard, reports were identified using the name of the active ingredient in the "suspected drugs" field. All reports identified were retrieved and classified according to the indication of use (COVID-19 and others/unknown), the organ/system of the ADR, country, and other suspected concomitant drugs prescribed to patients with COVID-19 (reports with two or more drugs analyzed for COVID-19 in the "suspected drug" field).

To identify adverse hepatic reactions, we considered the adverse events associated with the hepatobiliary disorder system according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system and liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]).

Altered liver enzyme levels were classified as described in the Investigation of MedDRA classification of adverse events and all liver events belonging to the hepatobiliary disorder system.

Database

The FAERS Public Dashboard is an open-access database documenting reports of suspected ADRs coordinated by the FDA (Food and Drugs Administration, 2020). FAERS receives voluntary, spontaneous notifications

of adverse events, medication errors, and quality deviations forwarded by health professionals and consumers (Food and Drugs Administration, 2020). The FAERS Public Dashboard is an interactive and easy-to-use tool that aims to extend access to FAERS data to the general public to facilitate investigations into adverse events reported to the FDA since 1968 (Food and Drugs Administration, 2020).

Disproportionality analysis

A detailed analysis was conducted using all reports of liver events belonging to the hepatobiliary disorder system and hepatitis, according to the MedDRA classification system. Disproportionality analysis was performed to determine the reported odds ratios (RORs) and their 95% confidence intervals (95% Cis) in the following scenarios:

S1) a potential increase in the risk of reporting liver ADRs and hepatitis, comparing reports for patients with COVID-19 and those without COVID-19 for tocilizumab, hydroxychloroquine, and L/r.

S2), a potential increase in the chance of reporting liver ADRs in patients with COVID-19 for each drug analyzed when compared with other drugs prescribed to patients with COVID-19.

To analyze the impact of COVID-19 severity and concomitant use of two or more COVID-19 drugs, the ROR was determined in two additional scenarios:

S3), a potential increase in the chance of reporting liver ADRs between tocilizumab and/or remdesivir, given that these two agents have been used in severe cases (hospitalized) of COVID-19 (Montastruc*,* Thuriot, Durrieu, 2020);

S4), a potential increase in the chance of reporting liver ADRs with the concomitant use of drugs prescribed for treating COVID-19.

The ROR of a drug-ADR combination was defined as the ratio between the proportion of reports including the ADR of interest in the "case" group and reports including other ADRs in the "non-case" group. An association was considered statistically significant when the lower limit of the 95% CI exceeded 1.0 and the number of events was > 3 (Faillie, 2019). All analyses were performed using the counts of unique cases (single notifications identified by an identification number). Data processing and statistical analysis were performed using Microsoft Excel (version 16.0) and R software (version 4.0.2).

RESULTS

In total, we identified 3356 unique cases associated with the search terms "COVID-19," "coronavirus infection," or "SARS-CoV-2" in the "reason of use" field considering the four drugs analyzed. Of these notifications, 662, 1176, 744, and 1381 were listed under tocilizumab, remdesivir, L/r, and hydroxychloroquine as suspected drugs, respectively; among these, 556 notifications were associated with two or more suspected drugs used to treat COVID-19. ADRs were reported by health professionals, and the affected individuals were predominantly males, aged between 18 and 64 years. Although FAERS is a US-based database, it receives reports from numerous countries. Of the patient reports on COVID-19, 67.5% were from non-US countries, primarily Spain (21.4%) and France (16.5%). Considering tocilizumab, 36.1% (259/662) of reports indicated the concomitant use of drugs to treat COVID-19. Considering remdesivir, L/r, and hydroxychloroquine, the proportion of reports of suspected concomitant drug usage to treat COVID-19 was 0.6% (7/1176), 48.1% (358/744), and 39.0% (539/1381), respectively. Among reports including liver ADRs, the proportions were elevated for all drugs except remdesivir: 92.9% (156/168) for tocilizumab, 59.4% (253/426) for hydroxychloroquine, 43.6% (130/298) for L/r, and 0.0% (0/34) for remdesivir (Table I).

TABLE I - Characteristics of the reports of adverse drug events for remdesivir, tocilizumab, lopinavir-ritonavir, and hydroxychloroquine used to treat COVID-19 - reports received by Food and Drug Administration Adverse Event Reporting System (FAERS) Public Dashboard until June 2020

	Remdesivir				Tocilizumab				Lopinavir-Ritonavir				Hydroxychloroquine			
	Liver events		Non-liver events		Liver events		Non-liver events		Liver events		Non-liver events		Liver events		Non-liver events	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Reports COVID-19	34	100.0	1142	100.0	168	100.0	494	100.0	298	100.0	446	100.0	426	100.0	955	100.0
Sex																
Women	13	38.2	439	38.4	53	31.5	94	19	80	26.8	113	25.3	128	30	214	22.4
Men	20	58.8	696	60.9	105	62.5	270	54.7	206	69.1	279	62.6	272	63.8	482	50.5
N/A	1	2.9	7	0.6	10	6	130	26.3	12	4	54	12.1	26	6.1	259	27.1
Age (years)																
< 18	0	0	8	0.7	1	0.6	0	0	0	0	5	1.1	1	0.2	5	0.5
18 - 64	17	50	591	51.8	127	75.6	208	42.1	173	58.1	175	39.2	285	66.9	299	31.3
65 - 79	13	38.2	399	34.9	28	16.7	128	25.9	90	30.2	176	39.5	86	20.2	278	29.1
> 80	3	8.8	125	10.9	1	0.6	18	3.6	23	7.7	41	9.2	26	6.1	97	10.2
N/A	1	2.9	19	1.7	11	6.5	140	28.3	12	4	49	11	28	6.6	276	28.9
Suspected concomitant drug																
Hydroxychloroquine	0	0	0	0	130	77.4	61	12.3	104	34.9	193	43.3	173	40.6	669	70.1
Lopinavir-Ritonavir	0	0	0	0	7	4.2	4	0.8	168	56.4	218	48.9	104	24.4	193	20.2
Remdesivir	34	100	1135	99.4	0	0	6	1.2	0	0	0	0	0	0	0	0
Tocilizumab	0	0	6	0.5	12	7.1	391	79.1	7	2.3	4	0.9	130	30.5	61	6.4
Tocilizumab and hydroxychloroquine	0	0	1	0.1	-	-	-	-	19	6.4	31	7	-	-	-	-
Tocilizumab and lopinavir-ritonavir	0	0	0	0	-	-	-	-	-	-	-	-	19	4.5	31	3.2
Hydroxychloroquine and lopinavir-ritonavir	0	0	0	0	19	11.3	31	6.3	-	-	-	-	-	-	-	-
Hydroxychloroquine and remdesivir	-	-	-	-	0	0	1	0.2	0	0	0	0	-	-	-	-
Remdesivir and tocilizumab	-	-	-	-	-	-	-	-	0	0	0	0	0	0	1	0.1

Table II presents the RORs and the number of liver events, hepatitis, and increased liver enzymes for each drug, comparing the notifications associated with COVID-19 versus notifications for other indications or

unknown use. Comparing patients with and without COVID-19, the risk of reporting liver events was greater for hydroxychloroquine (ROR, 9.07; 95% CI, 8.0–10.29) than for L/r (ROR, 6.12; 95% CI, 5.22–7.17) or tocilizumab (ROR, 6.32; 95% CI, 5.28–7.56) Table II and Figure 1). Both hydroxychloroquine and L/r exhibited greater risks of liver events than other drugs of interest. Furthermore, hydroxychloroquine and tocilizumab presented statistically significant differences in hepatitis reports. Given that remdesivir is primarily employed to treat COVID-19, its use cannot be compared with other indications.

TABLE II - Comparison of the reported adverse liver reactions (including increased liver enzymes) for drugs used to treat patients with and without COVID-19 - reports received by Food and Drug Administration Adverse Event Reporting System (FAERS) Public Dashboard until June 2020

Drug	Adverse drug reactions	Reports		ROR
		COVID-19	Other uses or unknown use	
		n (%)	n (%)	
Tocilizumab	ALT Increased	18 (2.72)	439 (0.93)	2.99 (1.85 – 4.82)
	AST Increased	13 (1.96)	367 (0.77)	2.57 (1.47 – 4.49)
	Hepatitis	124 (18.73)	324 (0.68)	33.37 (26.76 - 47.86)
	All liver events	168 (25.38)	2420 (5.11)	6.32 (5.28 – 7.56)
	Total notifications	662 (100.00)	47374 (100.00)	Not applicable
Remdesivir	ALT Increased	164 (13.95)	15 (12.71)	Not applicable[a]
	AST Increased	130 (11.05)	12 (10.17)	Not applicable[a]
	Hepatitis	1 (0.085)	0 (0.00)	Not applicable[a]
	All liver events	34 (2.89)	2 (1.69)	Not applicable[a]
	Total	1176 (100.00)	118 (100.00)	Not applicable[a]
Lopinavir/ritonavir	ALT Increased	9 (1.21)	207 (1.82)	0.66 (0.34 – 1.29)
	AST Increased	20 (2.69)	201 (1.77)	1.54 (0.96 – 2.45)
	Hepatitis	31 (4.17)	147 (1.29)	3.32 (2.24 - 4.93)
	All liver events	298 (40.05)	1121 (9.85)	6.12 (5.22 - 7.17)
	Total	744 (100.00)	11383 (100.00)	Not applicable
Hydroxychloroquine	ALT Increased	13 (0.94)	322 (1.03)	0.91 (0.32 – 1.59)
	AST Increased	5 (0.36)	266 (0.85)	0.51 (0.23 – 1.14)
	Hepatitis	220 (15.93)	228 (0.73)	25.71 (21.17 - 31.22)
	All liver events	426 (30.85)	1460 (4.69)	9.07 (8 - 10.29)
	Total	1381 (100.00)	31161 (100.00)	Not applicable

ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase

a) Remdesivir was used primarily to treat COVID-19 and cannot be compared with other indications of use.

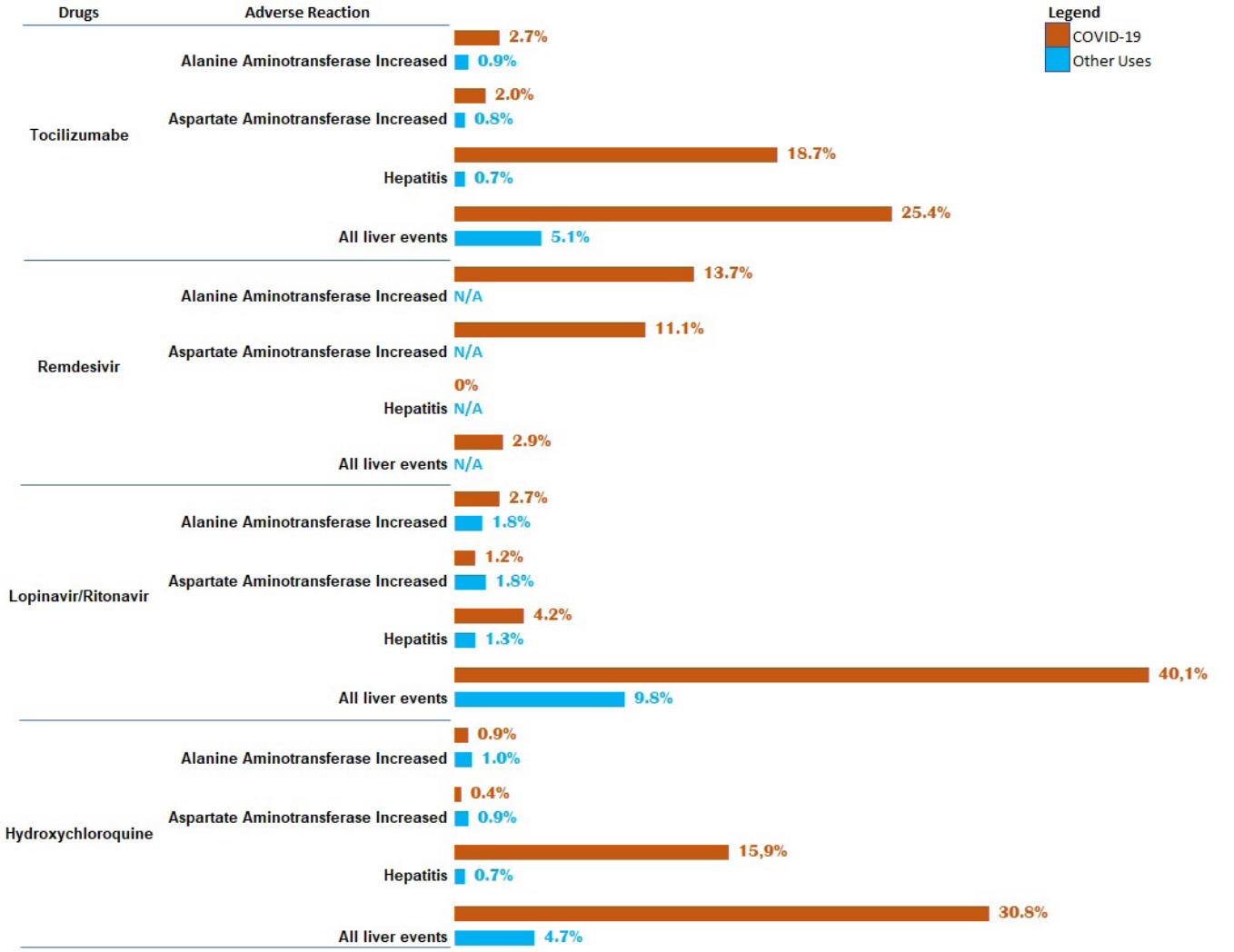

FIGURE 1 – Proportion of reports comprising adverse drug reactions – reports received by the Food and Drug Administration Adverse Event Reporting System (FAERS) Public Dashboard until June 2020.

We next compared monotherapy and combination therapy to treat COVID-19. As shown in Table III and considering reports on single drug use, remdesivir did not present an increased risk of liver events when compared with tocilizumab, hydroxychloroquine, and L/r (ROR, 0.08; 95% CI, 0.05–0.11). Nevertheless, remdesivir was associated with the highest number of reported liver alterations (164 for ALT and 130 for AST). Additionally, the risk of reporting elevations in ALT and AST was greater with remdesivir than with all other drugs used to treat COVID-19 (ROR, 13.43; 95% CI, 8.82–20.44; ROR, 7.62; 95% CI, 5.21–11.14, respectively).

TABLE III - Disproportionality analysis of the reports for remdesivir, tocilizumab, lopinavir-ritonavir, and hydroxychloroquine used to treat COVID-19 - reports received by Food and Drug Administration Adverse Event Reporting System (FAERS) Public Dashboard until June 2020

Drug	All adverse liver events ROR (CI 95%)	Hepatitis ROR (CI 95%)	ALT Increased ROR (CI 95%)	AST Increased ROR (CI 95%)
Hydroxychloroquine vs L/r, tocilizumab and remdesivir	3.54 (2.96 – 4.24)	31.00 (17.26 – 55.67)	0.10 (0.05 - 0,17)	0.04 (0.02 - 0.10)
L/r vs hydroxychloroquine, tocilizumab and remdesivir	4.33 (3.60 - 5.21)	0.36 (0.25 - 0.53)	0.16 (0.08 - 0.32)	0.47 (0.29 - 0.76)
Tocilizumab **vs** hydroxychloroquine, L/r, and remdesivir	1.57 (1.29 - 1.92)	5.52 (4.20 - 7.26)	0.41 (0.25 - 0.67)	0.33 (0.19 - 0.59)
Remdesivir vs hydroxychloroquine, L/r, and tocilizumab	0.08 (0.05 - 0.11)	Not applicable[a]	13.43 (8.82 - 20.44)	7.62 (5.21 - 11.14)
Tocilizumab vs Remdesivir				
Tocilizumab (all) vs Remdesivir	11.35 (7.74 - 16.66) [b]	Not applicable[a]	0.17 (0.11 - 0.29)	0.16 (0.09 – 0.29)
Tocilizumab (alone) vs Remdesivir	1.02 (0.53 – 2.00)	Not applicable[b]	0.23 (0.12 - 0.43)	0.22 (0.13 – 0.39)
Tocilizumab + Hydroxychloroquine				
Tocilizumab + Hydroxychloroquine vs Remdesivir	53.85 (34.85 - 82,08)	Not applicable[a]	0.08 (0.02 - 0.25)	0.03 (0.00 - 0.24)
Tocilizumab + Hydroxychloroquine vs Tocilizumab alone or associated with L/r and/or remdesivir	33.81 (19.94 - 57.34)	80.30 (32.09 – 200.92)	0.34 (0.10 - 1.18)	0.14 (0.02 – 1.09

ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; L/r = Lopinavir/Ritonavir

a) Could not be calculated because the occurrence of hepatitis with remdesivir in patients with COVID-19 was < 3.

b) Contamination by other drugs for COVID-19: 156 of 168 reports of liver events indicated that tocilizumab was one of two suspected drugs used to treat COVID-19.

Considering all reports of tocilizumab prescribed to treat COVID-19 with notifications for remdesivir, tocilizumab was associated with a high risk of reported liver disorders (ROR, 11.35; 95% CI, 7.74–16.66). However, on removing reports of other suspected drugs, the observed result no longer exhibited statistical significance (ROR, 1.02; 95% CI, 0.53-2.00). The use of hydroxychloroquine alone or combined with L/r was documented in 149 (88.7%) reports (Table I). Considering FAERS, the reports highlighted the greater risk of developing liver reactions with tocilizumab combined with hydroxychloroquine than with remdesivir or any other drug or combination used to treat COVID-19.

DISCUSSION

Given that COVID-19 is a new disease, its clinical manifestations, risk factors, and evolution remain poorly understood. Furthermore, the potential adverse effects of drugs used to manage patients with COVID-19 are yet to be comprehensively explored, and their impact should be carefully analyzed. The lack of etiologic treatment for COVID-19 has led to the use of various individual

therapeutics and drug combinations without established therapeutic efficacy, such as hydroxychloroquine and L/r, in countries like Brazil. The off-label use of these drugs without known efficacy in COVID-19 can endanger patient safety. In addition to offering no clinical benefit, prescribing off-label and non-effective drugs increases the risk of serious ADRs that can exacerbate the underlying disease and hinder patient recovery. Moreover, the off-label use of drugs approved by regulatory agencies for other indications can afford the prescriber a false sense of security.

In the present study, we aimed to identify suspected ADRs related to tocilizumab, remdesivir, hydroxychloroquine, and L/r reported in the FAERS, a large open pharmacovigilance database, and confirm an increased risk of reporting liver events and hepatitis on using these drugs to treat COVID-19. It should be noted that comparing the profiles of reports did not suggest differences in the potential hepatotoxicity risk owing to patient characteristics. Therefore, three hypotheses might explain the observed differences: (1) increased hepatotoxicity risk due to COVID-19; (2) drug-drug interactions between the specific therapies used for disease management; or (3) increased awareness of health professionals, given the novelty of COVID-19 and treatments yet to be corroborated with rational evidence. However, the use of remdesivir could not be subjected to all analyses, given that numerous reports failed to include the indication of its use (118 of 1294).

The number of reports describing hepatitis associated with the use of tocilizumab and hydroxychloroquine was greater when used for COVID-19 than for other indications. It should be highlighted that a high number of reports documented hepatitis in patients with COVID-19 within this brief period. Notably, most patients with liver damage and hepatitis associated with tocilizumab had received concomitant hydroxychloroquine therapy; therefore, the chance of reporting hepatotoxicity and hepatitis was greater with this drug combination than with other combinations used to manage COVID-19, with the ROR exceeding 30 for liver damage and 80 for hepatitis. Overall, these results suggest that although not considered a hepatotoxic drug, hydroxychloroquine combined with tocilizumab could potentiate the risk of hepatotoxicity, particularly hepatitis.

The risk of reporting liver reactions and hepatitis was greater with hydroxychloroquine than that with other drugs, with 59.4% of reports on hydroxychloroquine use and liver reactions documenting concomitant drug therapy. Additionally, L/r appeared more likely to induce liver-related reactions. Moreover, 43.6% of reports included the use of other medications. Importantly, tocilizumab was associated with the greatest proportion (92.9%) of liver reactions when used with other drugs, most frequently in combination with hydroxychloroquine (88.7%). Concerns regarding the risk of tocilizumab-induced hepatotoxicity have been previously outlined in another study using FAERS reports received until 2019 (Gatti *et al.,* 2020). Based on the findings of the present study, it can be suggested that the risk of tocilizumab-induced hepatotoxicity might be considerably higher among patients with COVID-19 than in those without COVID-19, particularly when combined with hydroxychloroquine. An evaluation of the Brazilian Spontaneous Notification System revealed that, among the drugs used in patients with COVID-19, hydroxychloroquine could be associated with the highest proportion of elevated transaminases (7.5%) (Melo *et al.,* 2021). A case series has recorded the occurrence of hepatic adverse events in patients with COVID-19 who were treated with tocilizumab after initial treatment with hydroxychloroquine and azithromycin (Serviddio *et al*., 2020). Thus, the findings of the present study corroborate previous evidence regarding the risk of hepatotoxicity associated with tocilizumab, hydroxychloroquine, and the combination of these two drugs.

Remdesivir is the only drug with few reports of concomitant use. Based on our analysis, the risk of reporting hepatotoxicity was substantially lower with remdesivir than that with the other drugs; however, this result could be influenced by the low tendency to employ remdesivir as part of a drug combination. Our results might seem contradictory with those of others based on the VigiBase database, given that the authors concluded that remdesivir was associated with a greater risk of hepatic events than tocilizumab (ROR, 1.60; 95% CI, 1.13–2.27) (Montastruc*,* Thuriot, Durrieu, 2020). Nevertheless, it should be noted that the authors had focused on hepatic lesions, and the reaction "increased

liver enzymes" represented 88% of the reported hepatic ADRs (Montastruc*,* Thuriot, Durrieu, 2020). In contrast, the FAERS database (and, subsequently, our analysis) assessed the risk of hepatic injury. Indeed, the number of reports describing "increased liver enzymes" among patients treated with remdesivir was high, probably attributed to the recent introduction of this drug in clinical practice.

Analyses of large pharmacovigilance databases have several limitations based on the reporting method and quality of the information provided in the reports. Accordingly, we performed a disproportionality analysis, a widely accepted method for identifying possible signals for further study (Michel *et al.,* 2017; Almenoff *et al.,* 2007; Dias *et al.,* 2015). Although large experimental and observational studies have not been conducted, signals raised through pharmacovigilance databases are useful for alerting clinicians, allowing the close follow-up of patients treated in real-world conditions. In addition, comparing results between various pharmacovigilance databases can be important in uncertain scenarios. Our study indicates that patients with COVID-19 could have a higher chance of reporting hepatic adverse events than those who used the evaluated drugs for other indications.

Additionally, our results highlight the importance of careful selection when prescribing any drug (new or old) to patients with COVID-19, with a special emphasis on prescribing combination therapy. The European Medicines Agency recommends that remdesivir should not be used with other hepatotoxic drugs and that hepatic function monitoring is required during treatment (European Medicines Agency, 2020a). The elevated risk of reporting adverse liver events in patients with COVID-19 who receive these drugs, alone or in combination, underlines the need for careful drug selection and efforts to reduce drug combinations in the absence of established benefits. Despite the uncertainties surrounding a new disease, systematic and widespread use of drugs without known efficacy should be avoided. The increased risk also emphasizes the importance of reporting any suspected adverse event to contribute to general knowledge, especially in the face of a new disease such as COVID-19, where several new drugs might be employed in poorly studied conditions.

CONCLUSION

The results of the present study revealed a high risk of adverse liver reactions in patients with COVID-19 who received tocilizumab, lopinavir/ritonavir, and hydroxychloroquine alone or in combination. These findings underscore the need for hepatic monitoring in patients with COVID-19 taking off-label medications. Additionally, the results strengthen the need for careful drug selection and an effort to reduce drug combinations if notable benefits are yet to be established.

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