Gastroenterology and Hepatology From Bed to Bench.

BRIEF REPORT

Hepatic disorders associated with the use of Ivermectin for SARS-CoV-2 infection in adults: a pharmacovigilance study in VigiBase

Teodoro J. Oscanoa[1,2,3], José Amado[3], Roman Romero-Ortuno[4,5], Alfonso Carvajal[6]

[1] *Universidad de San Martín de Porres, Facultad de Medicina Humana, Centro de Investigación de Seguridad del Medicamento, Lima, Perú*

[2] *Hospital Almenara ESSALUD, Lima, Perú*

[3] *Universidad Nacional Mayor de San Marcos, Facultad de Medicina, Lima, Perú*

[4] *Discipline of Medical Gerontology, Mercer's Institute for Successful Ageing, St James's Hospital, Dublin, Ireland*

[5] *Global Brain Health Institute, Trinity College Dublin, Ireland*

[6] *Centro de Estudios sobre la Seguridad de los Medicamentos (CESME), Universidad de Valladolid, Valladolid, Spain*

ABSTRACT

Aim: The aim of the present study was to review in VigiBase the reports of serious hepatic disorders associated with the use of ivermectin for COVID-19 in adults.

Background: In the face of the global health emergency caused by SARS-CoV-2, ivermectin, among other drugs, has been repurposed in some Latin American countries to treat COVID-19. Studies are needed on the safety of ivermectin for this new indication. VigiBase is the WHO pharmacovigilance database that registers all individual case safety reports (ICSRs) from more than 130 countries.

Methods: We extracted the ICSRs of men or women aged ≥ 18 years and dated between 1 January 2020 and 7 March 2021 which included an association with the use of ivermectin.

Results: Of 1393 ICSRs associated with ivermectin, 60 (4.3%) were registered as "serious." Ivermectin had been used for COVID-19 in 25 of those cases. Among the latter, 6 experienced hepatic disorders (hepatitis, hepatocellular injury, cholestasis, increased alanine aminotransferase and/or aspartate aminotransferase levels, abnormal liver function tests).

Conclusion: The safety of the use of ivermectin should be studied more exhaustively, especially as regards the possibility of hepatic disorders developing when the drug is used for COVID-19.

Keywords: Ivermectin, COVID-19, Drug-induced liver injury, Adverse drug reaction, SARS-CoV-2, Liver injury.

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Introduction

With its catastrophic health and economic consequences, the coronavirus disease 2019 (COVID-19) pandemic has posed unprecedented challenges to science and instigated a race against time to find efficacious treatments. One of the most important achievements has been the obtention of specific vaccines in record time; however, during the pandemic, about 100 drugs, mostly long-standing ones, have been proposed to be repurposed for this new indication (1). One such drug is ivermectin. Ivermectin was first isolated in 1974 from *Streptomyces avermitilis* (*S. avermectinius*) in Japan. Since then, it has been used in the treatment of certain parasitoses (helminthiasis), such as filariasis, *Strongyloides stercoralis*, and *Sarcoptes scabiei* infestation, among other indications (2). In April 2020, Caly et al. published a study conducted on Vero-hSLAM (Vero cells stably expressing human signaling lymphocyte activation molecules) cells in which

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Reprint or Correspondence: **Teodoro J. Oscanoa,** *Facultad de Medicina, Universidad Nacional Mayor de San Marcos. Drug Safety Research Center, Facultad de Medicina Humana, Universidad de San Martín de Porres. Hospital Almenara, ESSALUD, Lima, Perú.*

E-mail: tjoscanoae@gmail.com, toscanoae@usmp.pe

ORCID ID: 0000-0001-9379-4767

ivermectin had anti-viral activity against SARS-CoV-2 (3). Based on these findings along with those of ecological and observational studies, some Latin American countries included ivermectin as part of their drug strategies to face the epidemic (4). The use of ivermectin for COVID-19 prevention or treatment has particularly been encouraged in Perú, Bolivia, and Guatemala (5). Two meta-analyses published on the effectiveness of ivermectin in COVID-19 reported conflicting results (6, 7); regarding safety, no adverse reactions were recorded in the included studies.

In developing countries and for more than 30 years, ivermectin has been used by more than 300 million people annually for the control of human helminthiasis on a global scale. Currently, it is considered among the most relevant public health interventions in the developing world (8, 9). Therefore, knowing the safety aspects when it is administered in massive form and for new indications such as SARS-CoV-2 infection is of great interest. Ivermectin-associated hepatoxicity was described before the COVID-19 pandemic, but is extremely rare (10, 11); however, data on serious hepatotoxicity for COVID-19 indication is not known. Therefore, the current study reviewed the prevalence of serious hepatic disorders in adults associated with the use of ivermectin for COVID-19.

Methods

VigiBase is the WHO pharmacovigilance database that registers all individual case safety reports (ICSRs) entered by the National Pharmacovigilance Centers of more than 130 countries around the world. We conducted a search of this database using Vigilyze, a VigiBase analysis instrument that allows access to ICSRs. For the purpose of this study, we extracted all ICSRs associated with ivermectin registered as "serious" (12) between 1 January 2020 and 7 March 2021 in men or women aged ≥ 18 years. ICSRs in patients with age and sex unknown or medication errors were excluded. According to the Uppsala Drug Monitoring Center glossary, a serious reaction is an "adverse event or reaction that results in death, requires hospitalization or extension of hospital stay, results in persistent or significant disability or incapacity, or is life-threatening." We then selected "hepatic disorders" in those cases in which ivermectin had been indicated for COVID-19. We described the main characteristics of patients (age, sex) and type of adverse drug reaction (ADR) classified according to the Standardized MedDRA Queries (SMQs).

Results

During the study period, there were 1,393 ICSRs registered in VigiBase that were associated with ivermectin, of which 60 (4.3%) were registered as serious. In 35 cases, ivermectin was indicated in *scabies* (6), *strongyloidiasis* (6), filariasis (2), *elephantiasis* (1), *onchocerciasis* (1), *rosacea* (2), lice infestation (1), or "parasitic infection" (4), and the indication was not reported in 12 cases. In 25 cases, ivermectin had been indicated for COVID-19. Out of those 25, there were 6 reported serious cases of hepatic disorders (hepatitis, hepatocellular injury, cholestasis, increased alanine aminotransferase and aspartate aminotransferase, abnormal liver function tests). Four patients were male, and the overall mean age was 53.8 + 15.8 years. Ivermectin was administered during a mean of 2.2 + 2.2 days, and the mean daily dose was 13.8 + 2.7 mg. Three patients simultaneously received other drugs (remdesivir, hydroxychloroquine, azithromycin, tocilizumab). Two patients had concurrent conditions (strongyloidiasis, diabetes mellitus) (Table 1). Liver enzyme data was reported only in 2 patients. In all patients, the evolution was favorable after stopping the drug (de-challenge), and no patient was re-exposed (re-challenge). Causality analysis was reported in 3 cases, qualifying as possible or probable (Table 1). Table S1 in the supplementary file describes the 19 non-hepatic serious adverse reactions associated with ivermectin use for COVID-19.

Discussion

The present study described six cases reported in VigiBase of serious hepatic disorders in adults who used ivermectin for SARS-CoV-2 infection. Even though the absolute numbers involved are low, more studies are required on the hepaitic safety of this drug when it is used for COVID-19.

Before the COVID-19 pandemic, ivermectin-induced liver injury was considered as very rare, consisting mostly of mild to moderate elevations in liver enzyme levels (13). Guzzo et al. studied the tolerability and pharmacokinetics of escalating doses of

Table 1. Hepatic disorders with the use of ivermectin for SARS-COV2 infection.

Age /Sex	Ivermectin: duration (days)	Ivermectin: daily dose (mg)	Standardised MedDRA Queries (SMQs) classification	Other suspect drugs	Concurrent conditions	Causality analysis	Outcome
61/F	NR	15	Liver function test abnormal	NR	NR	NR	Recovering
48 /M	6	NR	ALT (266 U/L) and AST increased	Hydroxychloroquin, Azithromycin	Diabetes mellitus	WHO-UMC Causality: Possible	Recovered with sequelae
62/M	2	12	GGTP increased (115 U/L)	NR	NR	WHO-UMC Causality: Probable/Likely	Recovered
73/F	1	18	Hepatocellular injury, Cholestasis	Remdesivir	NR	WHO-UMC Causality: Possible	Recovered
52/M	1	12	Hepatitis	Hydroxychloroquine, Tocilizumab	*Strongyloidiasis*	NR	Recovered
27/M	1	12	Hepatitis	Hydroxychloroquine, Tocilizumab	NR	NR	Recovering

*Individual Case Safety Reports (ICSRs) registered in Vigibase® between 1 January 2020 and 7 March 2021 according to Standardised MedDRA Queries (SMQs) classification. M: male; F: female; NR: not reported; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGTP: gamma-glutamyl transferase; WHO-UMC: World Health Organization – Uppsala Monitoring Centre.

ivermectin in healthy adults, finding that 2/30 subjects with doses of 30 mg developed elevations of more than 2 times alanine aminotransferase and gamma-glutamyl transferase baseline levels; however, doses up to 60 mg did not increase the risk of liver injury (14). On the other hand, susceptibility to hepatotoxicity may be higher in animals, such as rabbits, in which degenerative changes of the liver have been described (15).

In 2006, Veit et al. reported the first case of ivermectin-induced liver injury in a 20-year-old woman originally from Cameroon who was infected by the L. loa parasite, in which a liver biopsy showed intralobular inflammatory infiltrates, confluent necrosis and apoptosis (10). In 2011, Hirote et al. in Japan reported another case of ivermectin-induced liver injury in an 85-year-old homeless man with scabies who received a dose of 0.2 mg/Kg of body weight in 2 doses with an interval of 15 days, where alanine aminotransferase levels were up to 1081 (Normal value: 100-325 IU/L); transaminase and bilirubin levels returned to normal levels only 10 weeks after the start of therapy (11).

In the 5 ICSRs reviewed in our study, ivermectin was the only drug suspected of adverse reaction in two patients. One patient received ivermectin and remdesivir, and the reported adverse reaction was hepatocellular injury and cholestasis. In relation to remdesivir, a meta-analytic study reported a 1% discontinuation due to hepatotoxicity in COVID-19 patients and a frequency of bilirubin elevation of 4% (16, 17). Montastruc et al. described 130 remdesivir-induced hepatic disorders reported in VigiBase (18). The administration of ivermectin to a patient with COVID-19 should be accompanied by adequate monitoring of liver enzymes, especially in patients with previous liver disease such as cirrhosis (19).

One of the limitations of the present study is that the ICSRs reviewed in VigiBase do not have sufficient data to complete the drug-induced liver injury (DILI) criteria (DILI Expert Working Group) (20). On the other hand, it has been reported that 21% of COVID-19 patients had liver injury during hospitalization and that the use of lopinavir / ritonavir increased the odds of liver injury by 4-fold (21). Therefore, to classify a case as DILI due to ivermectin, a causality analysis is necessary with specific instruments such as RUCAM (Roussel Uclaf Causality Assessment Method) (22). The cases described herein should be taken as a case of need for a broader investigation on the possible hepatotoxicity of ivermectin when it is used for COVID-19. The conclusion of our analysis and our recommendation do not necessarily represent the opinion of the World Health Organization.

Conclusion

In conclusion, the present study suggests that ivermectin may induce serious hepatic disorders when used in patients with COVID-19, which may further complicate the clinical outcome of these patients. Close monitoring of COVID-19 patients receiving ivermectin is necessary, particularly in patients with other risks for hepatic injury such as pre-existing liver disorders and the concomitant use of hepatotoxic drugs.

Conflict of interests

The authors declare no conflict of interest.

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