Original Article

Ivermectin-Induced Liver Injury Due to Self-Medication in SARS-CoV-2 Infection

Teodoro J. Oscanoa[1,2,3*ID], José Amado-Tineo[3,4], Javier Matta-Pérez[4], Waldo Taype-Huamaní[4], Alfonso Carvajal[5], Roman Romero-Ortuno[6]

[1] Universidad de San Martin de Porres, Facultad de Medicina Humana. Drug Safety Research Center, Lima Perú.
[2] Servicio de Geriatría, Hospital Nacional Guillermo Almenara, EsSalud, Lima, Perú.
[3] Universidad Nacional Mayor de San Marcos, Facultad de Medicina. Lima Perú
[4] Hospital Nacional Edgardo Rebagliati Martins, EsSalud, Lima Perú.
[5] Centro de Estudios sobre la Seguridad de los Medicamentos (CESME), Universidad de Valladolid, Valladolid, Spain.
[6] Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland

ABSTRACT

Background:
With the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic posing a global health emergency, self-medication with ivermectin has been observed in certain Latin American countries. This study aimed to characterize the clinical features of liver injury associated with ivermectin when used as self-medication for treating coronavirus disease 2019 (COVID-19).

Materials and Methods:
We reviewed the clinical records of patients diagnosed with severe COVID-19 at the Emergency Room of Rebagliati Hospital in Lima, Peru, in March 2021. The criteria of the Drug-Induced Liver Injury (DILI) Expert Working Group and the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) were utilized to establish the diagnosis of drug-induced liver injury and assess causality, respectively.

Results:
We report five cases of ivermectin-induced liver injury (IILI), comprising four men and one woman, with a mean age of 49.3±12.3 years. The mean daily dose, duration, and total dose of ivermectin were 32.9±21.8 mg/day, 2.6 ± 0.6 days, and 89.6±71.4 mg, respectively. On average, IILI occurred 11±3.8 days after the initiation of treatment, and none of the cases developed jaundice. The mean levels of alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase were elevated 8±4.4, 1.7±0.9, and 10.9±5.0 times above the upper limit of normal, respectively. Two patients exhibited a hepatocellular pattern, two had a mixed pattern, and one displayed a cholestatic pattern. All cases were classified as mild and achieved recovery. Causality assessment categorized four cases as "possible" and one case as "highly probable.".

Conclusion:
The findings emphasize the need for further pharmacovigilance studies on IILI when used for COVID-19 treatment.

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

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Corresponding author:
Teodoro J. Oscanoa, MD

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.
Address: Av. Alameda del Corregidor 1502, La Molina 15024. Lima, Perú.

Tel : + 513652300
Email: tjoscanoae@gmail.com , toscanoae@usmp.pe

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INTRODUCTION

Ivermectin, isolated from Streptomyces avermitilis 47 years ago, has been widely used as an effective treatment for human helminthiasis, particularly in low-income countries. Its usage has extended to over 300 million individuals annually (1). In April 2020, amidst the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a study was published revealing the findings of research conducted on Vero-hSLAM cells. The study demonstrated that ivermectin exhibited antiviral activity against SARS-CoV-2 (2). In April 2021, a living systematic review and network meta-analysis examining prophylaxis against coronavirus disease 2019 (COVID-19) was published. The review found no conclusive evidence regarding the effectiveness of ivermectin combined with iota-carrageenan or ivermectin alone in reducing the risk of SARS-CoV-2 infection. However, in terms of safety, no adverse reactions were reported in the studies included in the analysis(1,3) Prior to the initiation of mass vaccination, certain Latin American countries, including Peru, Bolivia, and Guatemala, considered the use of ivermectin as part of their strategy to combat the SARS-CoV-2 epidemic(4). Consequently, a significant increase in its consumption without medical prescription was observed(5), likely attributed to the scarcity of vaccines and the overwhelming strain on the healthcare systems in these South American nations(6). The utilization of ivermectin in Latin America during the COVID-19 pandemic has been a topic of controversy(7).

Ivermectin has been widely regarded as a safe drug due to its extensive use in controlling human helminthiasis in developing countries. However, it is crucial to thoroughly evaluate the safety considerations when administering it for a new indication, such as SARS-CoV-2 infection, which affects various organs in the human body. This is particularly important in cases where there is evidence of its consumption without a medical prescription. Although instances of ivermectin-associated hepatotoxicity have been reported prior to the COVID-19 pandemic, such occurrences are extremely rare (8,9). Hence, there is significant interest in investigating whether the use of ivermectin in patients with SARS-CoV-2 infection could potentially lead to drug-induced liver injury (DILI).

The aim of this study was to present five cases of liver injury induced by ivermectin when it was employed as a form of self-medication for the treatment of SARS-CoV-2 infection.

MATERIALS AND METHODS

This study presents a case series derived from patients admitted to the Emergency Service of Edgardo Rebagliati Martin National Hospital, EsSalud, which is a highly complex and renowned medical facility in Lima, Peru. The clinical records of patients diagnosed with severe COVID-19 in March 2021 were carefully reviewed for the purpose of this study.

Inclusion criteria

We reviewed the medical records of adult patients (aged 18 years and older) who presented with severe SARS-CoV-2 infection, as confirmed by molecular tests utilizing polymerase chain reaction with reverse transcription. Severe COVID-19 was defined as peripheral oxygen saturation below 93% (without supplemental oxygen) or lung involvement exceeding 30% on the total severity score (TSS) derived from lung computed tomography (CT) scans(10). For the diagnosis of ivermectin-induced liver injury (IILI) and the assessment of causality, the criteria established by the DILI-Expert Working Group and the Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) were employed, respectively(11). The CIOMS/RUCAM scale applies numerical weighting to key features in seven different domains: chronology (latency and dechallenge), risk factors, concomitant drug use, search for other etiologies, existing information on the drug's hepatotoxic potential, and response to rechallenge. The numerical weight given to each key feature is summed up to generate an overall score that reflects the causality probability (highly probable, probable, possible, unlikely, or excluded) (12).

Study variables

During the examination of medical records, various data points were extracted, including age, sex, qSOFA (quick Sequential Organ Failure Assessment) score at admission, and comorbidities such as type 2 diabetes mellitus, arterial hypertension, and obesity, among others. Additionally, information pertaining to the patient's outcome, whether it was hospital discharge or death, was recorded. Furthermore, data regarding lymphocyte count, D-dimer values, and serum ferritin levels were also gathered.

Statistical analysis

For data description, the mean and standard deviation were utilized, along with frequencies and percentages. In order to determine the extent of elevation of alanine aminotransferase (ALT) and alkaline phosphatase (AP) in the reported cases, the serum values of these enzymes were divided by the upper limit of normal (ULN).

Ethical aspects

This study received approval from the Research

Ethics Committee for COVID-19, as indicated by letter 676-GRPR-ESSALUD 2021. Adequate measures were implemented to ensure the privacy and confidentiality of patient information.

RESULTS

In this study, a total of 327 patients were included, out of which 38 individuals (11%) had self-medicated with ivermectin prior to their hospitalization. Among these 38 patients (five men, and four women), five were diagnosed with liver injury, which was presumed to be related to the use of ivermectin. The mean age of the patients was 49.3±12.3 years.

The mean values (standard deviation) of Tomographic Severity Score (TSS), C-reactive protein, ferritin levels, lymphocyte count, and D-dimer were as follows: TSS 52.2% ±22.6, C-reactive protein 13.8±12.2 mg/dL, ferritin levels 1325.4±239.7 ng/mL, lymphocyte count 2.0±2.0 K/UL, and D-dimer 0.9±0.7 Ug/mL.

Except for two patients (one with type 1 diabetes mellitus and the other with obesity), the remaining patients did not have any identified risk factors. The mean daily dose, duration, and total dose of ivermectin were 32.9±21.8 mg/day, 2.6±0.6 days, and 89.6±71.4 mg, respectively. On average, liver injury occurred 11±3.8 days after the initiation of treatment, and none of the patients developed jaundice. The mean levels of alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase were elevated 8±4.4, 1.66±0.9, and 10.9±5.0 times above the ULN, respectively. Two patients showed a hepatocellular pattern of liver injury, while two had a mixed pattern, and one displayed a cholestatic pattern. All cases were classified as mild and recovered.

Regarding exposure to other drugs apart from ivermectin, patient 1 received clavulanic acid after being hospitalized. Patients 4 and 5 took azithromycin after hospitalization, while patient 3 was exposed to levofloxacin after hospitalization. Patients 1, 2, and 4 had been exposed to acetaminophen prior to hospitalization, with doses lower than 2 g/day and for a maximum of two days. Causality assessment categorized four cases as "possible" and one case as "highly probable" (Tables 1 and 2).

Table 1. Clinical characteristics of ivermectin-induced liver injury associated with the use in SARS-CoV-2 infection by self-medication

Sex/Age	Comorbidities	Severity markers					Treatment					
		Tomographic Severity Score (TSS) (%)	C-reactive protein (mg/dL)	Ferritin (ng/mL)	Lymphocyte count (K/uL)	D-dimer (ug/mL)	Lactate dehydrogenase (LDH) (U/L)	corticosteroids	Heparin	Antibiotics	High-flow nasal oxygen (HFNO)	Mechanical
Patient 1: M/50	no	75	30.15	992	1363		376	Yes	Yes	Yes	Yes	No
Patient 2: F/55	no	40	4.89	1500	1430	0.5	725	Yes	Yes	No	Yes	No
Patient 3: F/32	Diabetes Mellitus type 2	20	11.49	Missing	690	0.5	250	Yes	Yes	Yes	Yes	No
Patient 3: M/65	Obesity	56	0.54	1309.5	1120	0.72	415	Yes	Yes	No	Yes	No
Patient 3: M/44	no	70	22.07	1500	5600	1.9	1534	Yes	Yes	Yes	Yes	Yes

Table 2. Ivermectin-induced liver Injury associated with the use in SARS-CoV-2 infection by self-medication

Sex/Age	Ivermectin			Time to Onset (days)	Hepatic enzymes				Type of injury	RUCAM assessment pattern	Other drugs	outcome
	Dose mg /day	Duration (days)	Total dose (mg)		ALT times above ULN	ALP times above ULN	Bilirubin (mg/dL)	GGT times above ULN				
Patient 1: M/50	25.2	3	75.6	12	5.39	3.23	0.91	15.43	cholestatic	possible	amoxicillin/ clavulanic acid (15 capsules), dexamethasone amp (2), acetaminophen, loratadine	Recovered
Patient 2: F/55	71.7	3	215	5	6.69	1.5	1.14	15	mixed	possible	Ceftriaxone (2 days), acetaminophen (2 days)	Recovered
Patient 3: F/32	24	2	48	13	6.58	1.47	1.79	6.9	mixed	possible	NPH insulin, Azithromycin 500 mg/day, 5 days, levofloxacin 500 mg/day, 5 days, and prednisone	Recovered
Patient 3: M/65	22.5	3	67.5	15	5.3	1	0.39	No reported	hepatocellular	possible	azithromycin, acetaminophen	Recovered
Patient 3: M/44	21	2	42	10	15.8	1.1	2.07	6.2	hepatocellular	highly probable	Azithromycin, vitamin C, Vitamin D	Recovered

Upper limit of the normal range (ULN), Roussel Uclaf Causality Assessment Method (RUCAM), ALT (alanine aminotransferase) and ALP (alkaline phosphatase) gamma-glutamyl transferase (GGT),

DISCUSSION

This study represents the first report of IILI in Latin America when utilized as a form of self-medication for SARS-CoV-2 infection. The key features of IILI observed in this study include a total dose of 89.6 mg and a duration of 2.6 days. The predominant patterns of liver injury were hepatocellular and mixed. Notably, all patients achieved complete recovery from the liver injury.

In South Africa, a 70-year-old female patient was reported with a case of IILI. She had been taking a dose of 12 mg/day for 3 weeks, resulting in a total dose of 252 mg. The pattern of liver injury was hepatocellular, and the causality analysis using the RUCAM score indicated a highly probable association between ivermectin and DILI. Fortunately, the patient experienced full recovery after a period of 3 months (13). In Baltimore, USA, another case was documented involving a patient with a schizophrenia-spectrum disorder who had been self-medicating with escalating daily doses of ivermectin for the past 6 months. In the days leading to admission, the patient had been taking up to 100 mg per day. This resulted in a diagnosis of fulminant liver failure, and the patient ultimately required a liver transplant (14). A case from Omaha, USA, involved a 61-year-old male patient with ischemic cardiomyopathy who had been self-administering weight-based horse ivermectin injections for COVID-19 prophylaxis. The

patient developed hepatic encephalopathy but eventually showed improvement and did not require a liver transplant (15). A study based on the analysis of cases reported in VigiBase, the WHO pharmacovigilance database, identified six cases of serious hepatic disorders associated with the use of ivermectin for COVID-19. These disorders included hepatitis, hepatocellular injury, cholestasis, increased alanine aminotransferase and/or aspartate aminotransferase levels, and abnormal liver function tests (15). Additionally, a study examining adverse events reported in the pharmacovigilance system database of Rebagliati Hospital in Lima, Peru, from April to October 2020, found that 14.3% of these notifications were related to hepatobiliary adverse events (16). Prior to the COVID-19 pandemic, only two cases of IILI had been reported(8,9).

A limitation of the present study is the need to differentiate between DILI) and abnormal liver function tests observed during hospitalization in patients with severe COVID-19. A separate study reported frequencies of increased levels of alanine aminotransferase (>3 times the ULN), alkaline phosphatase (>2 ULN), and gamma-glutamyl transferase (GGT, >3 ULN) at 10.4%, 0.7%, and 2-4% respectively. This study also demonstrated that using lopinavir/ritonavir significantly increased the risk of such abnormalities (17). In this context, it is essential to highlight that the criteria used in our study for the operational definition of DILI(11,18), help exclude the possibility of abnormal liver function tests being solely associated with severe COVID-19 (19). Another limitation is the potential association of DILI with other potentially hepatotoxic drugs, such as amoxicillin-clavulanate, azithromycin, levofloxacin, and acetaminophen, aside from ivermectin. However, no temporal relationship was identified between DILI and exposure to these drugs. It is known that amoxicillin-clavulanate-induced liver injury typically occurs in 98% of cases after 2 weeks of exposure to this antibiotic(20). Azithromycin-induced hepatotoxicity has been reported to manifest 1-3 weeks after initiation of azithromycin(21). Similarly, levofloxacin-induced hepatotoxicity generally arises 1-3 weeks after starting the drug (22). Furthermore, the exposure to acetaminophen in our study was at doses below 2g/day in adults and for a maximum duration of 2 days, which is not known to cause DILI (23).

In conclusion, the occurrence of IILI in the context of COVID-19 treatment highlights the need for additional pharmacovigilance studies. As evidenced by the cases reported in this study and other documented instances, there is a potential risk associated with the use of ivermectin in the treatment of COVID-19. The findings underscore the importance of closely monitoring and assessing the safety profile of ivermectin in this specific context. Further pharmacovigilance studies are necessary to gather more comprehensive data on the incidence, risk factors, mechanisms, and outcomes of IILI in patients with COVID-19. These studies can provide valuable insights to guide clinical decision-making and optimize patient safety in managing SARS-CoV-2 infection.

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Ethics Approval:

This study was approved by the Research Ethics Committee of Hospital Nacional Edgardo Rebagliati Martins, EsSalud, with the letter 676-GRPR-ESSALUD 2021 in Lima Perú.

Consent for Publication:

Not applicable. The necessary strategies were implemented to maintain the privacy of patient information.

Availability of Data and Material: none

Authors' Contribution

Data curation: José Amado-Tineo
Formal analysis: Teodoro J. Oscanoa
Funding acquisition: Not applicable.
Investigation: José Amado-Tineo, Waldo Taype-Huamaní , Javier Matta-Pérez,
Methodology: Teodoro J. Oscanoa, Alfonso Carvajal
Project administration: Teodoro J. Oscanoa
Resources: Not applicable.
Software: Not applicable.
Supervision: Roman Romero-Ortuno
Writing–original draft: Teodoro J. Oscanoa, Alfonso Carvajal
Writing–review & editing: Roman Romero-Ortuno

Conflict of interest:

The authors declare no conflict of interest related to this work.

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