Remdesivir-Induced Hepatotoxicity: A Systematic Review of Clinical Evidence, Pharmacokinetics, and Safety Concerns

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ABSTRACT

Background: *Remdesivir is widely used for the treatment of COVID-19, with its potential benefits currently under investigation. Concerns remain regarding its potential hepatotoxic side effects. Drug-drug interactions, specifically with CYP3A4 and P-glycoprotein inhibitors, may worsen hepatotoxicity. In this context, dexamethasone has been suggested to mitigate liver injury, but the role remains unclear. Therefore, this study aimed to explore the characteristics, mechanisms, and risk factors of remdesivir-induced hepatotoxicity through a systematic review of case reports.*

Methods: *A systematic review was conducted using databases such as PubMed, Scopus, EBSCO, and BMJ Case Reports for cases published from 2020 to 2024. The keywords used were "remdesivir," "hepatotoxicity," "COVID-19," and "liver failure." Relevant case reports were selected based on predefined inclusion and exclusion criteria. Furthermore, data were extracted following the Joanna Briggs Institute (JBI) checklist for case reports.*

Results: *Among 46 individual articles screened after the removal of duplicates, five that detailed a total of six patients were eligible for inclusion. Hepatotoxicity was frequently reported in elderly patients and those with chronic liver disease. Drug-drug interactions that include remdesivir and CYP3A4 inhibitors increased the risk of liver injury. Based on observation, dexamethasone was associated with reduced hepatotoxicity, primarily due to its anti-inflammatory effects. In patients with ALT >5× ULN, remdesivir administration was controversial. Some cases showed improvement, and others required discontinuation due to severe liver dysfunction.*

Conclusion: *This study emphasized the necessity for safety evaluations and standardized liver function monitoring in patients receiving remdesivir. Further investigation is essential to define clinical guidelines and improve patient safety in antiviral treatments.*

Keywords: *COVID-19, Drug-Induced Liver Injury, Hepatotoxicity, Liver Injury, Remdesivir*

ABSTRAK

Latar Belakang: *Remdesivir umum digunakan dalam pengobatan COVID-19, dan manfaat lainnya masih dalam penelitian. Namun, kekhawatiran mengenai efek samping hepatotoksiknya tetap menjadi perhatian. Interaksi obat dengan inhibitor CYP3A4 dan P-glikoprotein dapat memperburuk hepatotoksisitas. Deksametason diduga dapat mengurangi cedera hati, namun perannya masih belum jelas. Studi ini bertujuan*

untuk mengeksplorasi karakteristik, mekanisme, dan faktor risiko hepatotoksisitas akibat remdesivir melalui tinjauan sistematis laporan kasus.

Metode: *Tinjauan sistematis dilakukan dengan mengumpulkan data PubMed, Scopus, EBSCO, dan BMJ Case Reports untuk laporan kasus yang diterbitkan antara tahun 2020 hingga 2024. Kata kunci yang digunakan adalah "remdesivir," "hepatotoksisitas," "COVID-19," dan "gagal hati." Laporan kasus yang relevan dipilih berdasarkan kriteria inklusi dan eksklusi yang telah ditentukan sebelumnya. Ekstraksi data dilakukan melalui pedoman dari Joanna Briggs Institute (JBI) untuk laporan kasus.*

Hasil: *Dari 46 artikel individual yang dikumpulkan setelah penghapusan duplikat, lima studi yang merinci total enam pasien individu dinyatakan layak untuk diikutsertakan. Hepatotoksisitas sering dilaporkan pada pasien lanjut usia dan mereka yang memiliki penyakit hati kronis. Interaksi obat antara remdesivir dan inhibitor CYP3A4 meningkatkan risiko cedera hati melalui dua mekanisme. Deksametason dikaitkan dengan penurunan hepatotoksisitas, kemungkinan karena efek antiinflamasinya. Pada pasien dengan ALT >5× ULN, pemberian remdesivir masih menjadi perdebatan, dengan beberapa kasus menunjukkan perbaikan, sementara pada studi lain terjadi disfungsi hati yang parah.*

Kesimpulan: *Studi ini menekankan pentingnya evaluasi keamanan jangka panjang dan pemantauan fungsi hati yang terstandarisasi pada pasien dalam pengobatan remdesivir. Penelitian lebih lanjut diperlukan untuk mendefinisikan pedoman klinis dan meningkatkan keamanan pasien dalam pengobatan antivirus.*

Kata kunci: *COVID-19, Cedera Hati Akibat Obat, Hepatotoksisitas, Gagal Hati, Remdesivir*

INTRODUCTION

After a successful attempt using dexamethasone to treat COVID-19, very few antivirals have yet to be proven beneficial.[1] Remdesivir acts as an inhibitor of the viral RNA-dependent, and has inhibitory activity against Middle East Respiratory Syndrome and SARS-CoV-1, making it widely used during the global pandemic.[2,3] The drug was officially added to Indonesian national treatment guidelines for moderate-to-severe COVID-19 in August 2022. However, there is a lack of data regarding its safety and effectiveness after EUA approval.[4]

Remdesivir is a prodrug of a nucleotide analogue that interferes with RNA-dependent RNA polymerase, which disrupts virus genome replication and impairs proofreading mechanisms, hindering viral production.[5] The drug is the pioneering nucleoside analog designed to combat infections caused by respiratory viruses. Remdesivir showed clinical benefits and had a proven safety record. The absence of other effective treatments for COVID-19 suggests that its use will possibly extend beyond clinical trials and compassionate-use protocols into broader medical practice.[6] The use of remdesivir beyond COVID-19 is currently under further investigation, opening new possibilities for potential applications.[7,8]

This review discovered no significant difference between the remdesivir and placebo groups regarding treatment discontinuation due to adverse effects.[9] The use of remdesivir in patients with severely impaired kidney function also appeared to be well-tolerated.[10] However, the drug has been associated with liver injury, as evidenced by reports of elevated transaminase levels in patients.[11,12] The factors contributing to hepatotoxicity in COVID-19 patients, regardless of being caused by the medication or the disease, were unclear. To support future advancements in understanding the safety profile and associated risk, a systematic review of case reports detailing remdesivir-induced hepatotoxicity was conducted. This review aims to summarize collective clinical experiences with the adverse drug reaction and identify potential correlating factors.

METHODS

This systematic review was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO): CRD420251020623. Case reports documenting hepatotoxicity associated with remdesivir were sourced from PubMed, Scopus, Ebsco, and BMJ Case Report. The database search was restricted to peer-reviewed articles published in English between January 1, 2020, and December 31, 2024. The search strategy adopted keywords such as "remdesivir," "hepatotoxicity," or "liver failure" and "COVID-19" with similar approaches applied across all databases. Additionally, manual searches of article bibliographies were performed to identify further relevant reports. Inclusion

criteria required articles to report individual patient cases of hepatotoxicity associated with remdesivir treatment, without restrictions on age, ethnicity, or sex. Articles presenting only summarized data from multiple cases were excluded.

All necessary data were extracted and recorded in a pre-designed Excel sheet, which had been reviewed and approved by all authors. Only relevant studies that met the inclusion criteria were considered. Excluded materials included review articles, conference abstracts, articles that did not list individual cases, and non-English publications. The quality of all included outcomes was assessed for risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports/Case Series.[14] Any discrepancies in assessments were resolved through discussion, and data were extracted by a minimum of two authors to ensure accuracy and reliability.

RESULTS

A total of 54 articles were initially identified based on the selected keywords, with the screening and review process outlined in Figure 1. After removing duplicates, 46 articles remained for further evaluation. Title and abstract screening led to the exclusion of 38 articles. The primary reasons for exclusion included irrelevance to the study question, studies not concerning human subjects, and reviews. Additionally, three more articles were excluded, which comprised one review and two that did not report individual patient data. In this study, five articles were included as detailed in Table 1, all of which showed low risk of bias. The included case reports offered comprehensive clinical information on patient history, remdesivir treatment, outcomes, and follow-up, enabling a detailed evaluation of methodological evaluation. This consistent assessment method further enhanced the reliability and validity of the conclusions regarding remdesivir-related hepatotoxicity.

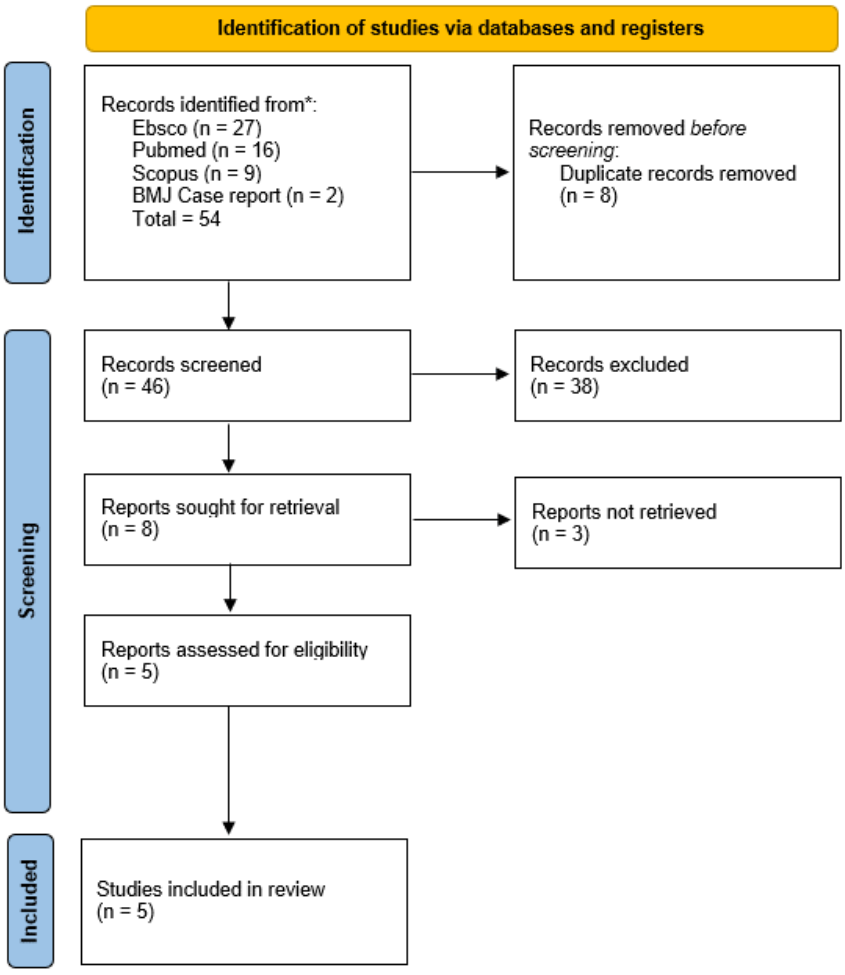

Figure 1. Article Selection

Table 1. Joanna Brigs Institute (JBI) Appraisal

Authors	Clear inclusion criteria	Standard, reliable measurement of condition	Valid methods for condition identification	Consecutive inclusion of participants	Complete inclusion of participants	Clear reporting of demographics	Clear reporting of clinical information	Clear reporting of outcomes/ follow-up	Clear reporting of presenting sites/clinics' demographics	Appropriate statistical analysis
Carothers et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/a
Leegwater et al. (2021)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	N/a
Dividis et al. (2021)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	N/a
Ahmed-Khan et al. (2023)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	N/a
Sabers et al. (2020)	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	N/a

Table 2. Summary of Patients Database

Study	No. of Patients	Age (Years)	Sex	Final Outcome
Ahmed-Khan et al. (2023)	1	69	Female	Death
Leegwater et al. (2021)	1	64	Male	Discharged
Dividis et al. (2021)	1	81	Male	Discharged
Carothers et al. (2020)	2	Case #1: 68	Female	Case #1: Discharged
		Case #2: 80	Female	Case #2: Death
Sabers et al. (2020)	1	82	Male	Discharged
Total/Median	6	74.5 (Range: 64 - 82)	4 Female, 2 Male	4 Discharged, 2 Deaths

This systematic review included five case reports detailing a total of six individual patients who experienced hepatotoxicity associated with remdesivir. The patients were predominantly elderly, with a median age of 74.5 years (range: 64–82 years). In this study, the cohort consisted of four female and two male patients. The outcomes varied, where four of the six being discharged and two experiencing fatal outcomes. The two deaths occurred among females aged 69 and 80. While these cases provided valuable initial insights, further large-scale studies were necessary to establish the definitive roles of age and sex as independent risk factors for mortality. A summary of the patients' database is presented in Table 2.

A study conducted by Ahmed-Khan et al. reported acute liver failure in 69 years 69-year-old female patient, resulting in mortality after 2 days of readmission. Remdesivir was given in a 200 mg loading dose and continued with 100 mg/day. After 4 days of therapy, the COVID-19 symptoms were resolved, and the patient was discharged. Upon readmission, new-onset transaminitis, encephalopathy, and elevated INR were observed. Despite negative toxicology for acetaminophen and ethanol, the patient was given intravenous N-acetylcysteine (NAC) with an initial dose of 150 mg/kg followed by 50 mg/kg over four hours, and 100 mg/kg for over 16 hours, totalling 300 mg/kg. The condition deteriorated over the following days and later resulted in death within a day.[15]

The possibility of drug interaction liver injury in patients with remdesivir was presented by Leegwater et al. A 64-year-old man positive for COVID-19 was hospitalized for oxygen therapy and chloroquine treatment. Due to respiratory failure, the patient was moved to the ICU for mechanical ventilation, complicated by pulmonary embolism and ICU-acquired weakness. On day 16, remdesivir was initiated but led to severe hepatotoxicity, establishing a temporal relationship and subsequent discontinuation while liver enzymes rapidly normalized. After 48 days, the patient was discharged to rehabilitation and returned 2 weeks later. The early hepatotoxicity of other drugs was excluded, which suggested remdesivir as the culprit.[16]

The influence of comorbidities on Remdesivir-associated liver injury was thoroughly explained by Dividis et al. An 81-year-old man was diagnosed with COVID-19 based on PCR and bilateral opacities on chest X-ray. Initial vitals were stable except for hypoxia (PaO_2: 66.7 mmHg, saturation: 88%). The patient was treated with remdesivir (200 mg loading dose, then 100 mg daily for 5 days), dexamethasone, and empirical antibiotics for suspected superinfection. New-onset atrial fibrillation was managed with enoxaparin and metoprolol, restoring sinus rhythm. After 48 hours, acute hepatocellular injury developed, with ALT rising from 61 to 1018 U/L and AST from 65 to 834 U/L, alongside coagulopathy (INR increased from 0.9 to 1.8). Imaging showed signs of congestive hepatopathy, including hepatic congestion and cardiac chamber

enlargement. Remdesivir was discontinued, and diuretics were initiated while liver enzymes gradually normalized over 9 days. The patient remained clinically stable and was discharged on day 11 without oxygen support.[17]

The possible role of NAC in mitigating severe hepatotoxic effects of remdesivir was described by Carothers et al. A 68-year-old woman with respiratory failure was diagnosed with COVID-19 pneumonia. Initially, a normal liver function was observed, while remdesivir was administered on day eight. By day 10, AST and ALT spiked to >5000 U/L, total bilirubin reached 3.1 mg/dL, INR increased to 2.3, and ammonia climbed to 161 µmol/L, reflecting acute liver failure. Remdesivir and amiodarone were discontinued, and an acetylcysteine infusion was initiated using the 21-hour protocol, which includes 150 mg/kg over 1 hour, 50 mg/kg over 4 hours, and 100 mg/kg over 16 hours. Based on observation, AST and ALT decreased to 235 and 966 U/L by day 14. The patient was discharged on Day 20, and the Liver function normalized by Day 24.[18]

Mortality was recorded despite the NAC protocol in the same facility. Second case of 80-year-old woman hospitalized for worsening COVID-19 pneumonia was treated with remdesivir (200 mg i.v. loading, then 100 mg i.v. daily for 4 days). On day 14, the patient developed acute liver failure (ALF) with AST/ALT rising to 2178/1510 U/L, total bilirubin of 2.1 mg/dL, INR of 1.7, and ammonia of 128 µmol/L. NAC infusion was given using the 21-hour protocol, and after 12 hours, AST/ALT improved to 546/871 U/L. Despite transient respiratory improvement, the patient developed septic shock, atrial fibrillation, metabolic acidosis, and hypoglycemia, leading to cardiac arrest and death.[18]

The decision to use remdesivir when the patient already has elevated liver enzymes should be studied cautiously and under strict monitoring. Sabers et al. detailed their case report on the administration of remdesivir in a patient with similar characteristics. The 82-year-old male presented with severe COVID-19, acute respiratory failure, and sepsis, with AST/ALT levels of 1526/1075 U/L. Despite concerns regarding hepatotoxicity, remdesivir was initiated alongside dexamethasone. The patient's transaminase levels peaked on hospital day two (AST: 2105 U/L, ALT: 1573 U/L) but later began to decline. On hospital day seven, AST had dropped to 39 U/L and ALT to 226 U/L. The condition improved with reduced oxygen requirements, and the patient was discharged on hospital day 10.[19] Clinical outcomes have been summarized in Table 3.

Table 3. Summary of Clinical Outcome

Study	Additional Therapy besides remdesivir	Days from remdesivir initiation to Hepatotoxicity	Comorbidities	Peak ALT (U/L)	Peak AST (U/L)	Peak INR	Peak Alk. Phos. (U/L)	Peak Total Bilirubin (mg/dL)	21-hour NAC Protocol	Days to Reach Normal Liver Function	Final Outcome
Ahmed-Khan et al.	N-Acetylcysteine, Prednisone	6 days	Not Reported	1347	2050	12.4	154	2.4	Yes	Not reached	Death
Leegwater et al.	Chloroquine	5 days	Pulmonary embolism, ICU-acquired weakness	1305	1461	Not Reported	269	8 µmol/L	No	Early rapid decrease followed by progressive decrease (Figure 1, Leegwater et al.)	Discharged
Dividis et al.	Dexamethasone, enoxaparin, metoprolol	2 days	Congestive hepatopathy, new-onset atrial fibrillation	1018	834	1.8	96	0.9 µmol/L	No	9 days after discontinuation	Discharged
Carothers et al. Case #1	Amiodarone (discontinued)	2 days	Respiratory failure	>5000	>5000	2.3	Not Reported	3.1	Yes	Normalized by day 24 (14 days after discontinuation)	Discharged
Carothers et al. Case #2	Convalescent plasma	9 days	Septic shock, atrial fibrillation, metabolic acidosis, hypoglycemia	1510	2178	1.7	109	2.1	Yes	Not reached (only transient improvement)	Death
Sabers et al.	Dexamethasone	Present at admission; peaked on day 2	Acute respiratory failure, sepsis	1573	2105	Not Reported	Not Reported	Not Reported	No	Declined during therapy; AST normal by day 7	Discharged

DISCUSSION

Remdesivir undergoes metabolism through both cytochrome P450 (CYP) enzymes and non-CYP pathways, including carboxylesterases.[20] Specifically, CYP3A4 is a broad-specificity isoenzyme in the CYP family, playing a role in metabolizing nearly 50% of all commercially available drugs.[21] It is highly expressed in both the liver and small intestines, with the intestinal content accounting for approximately 40% of the proportion in the liver.[22]

Inflammation induced by COVID-19 plays a crucial role in modulating CYP3A4 activity and contributing to drug-induced liver injury (DILI). Pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β can suppress Pregnane X Receptor (PXR) activity, leading to downregulation of CYP3A4 expression. This inhibition reduces the metabolism of drugs that rely on the enzyme, causing drug accumulation and increased toxicity, which significantly heightens the risk of hepatotoxicity. Furthermore, inflammation contributes to oxidative stress by promoting reactive oxygen species (ROS) production, impairing mitochondrial function, and inducing hepatocyte injury. The precise mechanism through which remdesivir induces liver injury remains unclear. However, it may include direct hepatocyte toxicity resulting from the inhibition of mitochondrial RNA polymerase.[15] This combination of inflammation-driven CYP3A4 inhibition, drug accumulation, and oxidative stress underscores the critical need for careful drug monitoring and personalized therapy to mitigate the risk of DILI in COVID-19 patients [23]

All of the cases presented in this review consist of patients of older age.[15-19] As individuals age and develop chronic diseases, liver size and hepatic blood flow decline. Consequently, the dosage of drugs that undergo extensive hepatic metabolism should be adjusted accordingly.[24] Pre-existing liver disease was suspected to increase severity of DILI. These results are similar to the DILIN Prospective Study, where DILI tends to be more severe in 10% of patients with pre-existing liver disease.[25-27] The condition was also described by Dividis et al., who suggest that liver congestion and hypoperfusion lead to reduced oxygen diffusion and hepatocyte atrophy, resulting in impaired hepatic metabolism, similar to the age-related mechanism being proposed.[17,24] The effect of CLD on the progression and outcomes of COVID-19 remains largely unknown.[28] Based on this review, the effect of hepatotoxicity monitored may originate from the DILI pathway rather than direct COVID-19 destruction.

Drug-drug interactions (DDI) may occur during the use of remdesivir. It is crucial to recognize that specific drugs or natural products are metabolized by CYP or non-CYP enzymes and can influence the metabolism of concurrently administered drugs by inducing or inhibiting metabolizing enzymes.[21] A simulation on DDI comprising remdesivir and medications for comorbid conditions shows that carbamazepine, phenytoin, amiodarone, voriconazole, diltiazem, and verapamil have a high potential for significant interactions. However, chloroquine presents a weaker effect on interaction with remdesivir.[29]

The case presented by Leegwater et al. postulated another mechanism by which DILI could happen through P-Glycoprotein Inhibitors.[16] A study review of a substrate of CYP3A4 interaction with an inhibitor of CYP3A4 and a strong inhibitor of P-gp resulted in increased Cmax and AUC of the drugs, which could reach toxic levels.[30] Taking this into account, there is a possibility that the case reported by Leegwater et al. had a higher level of unmetabolized remdesivir due to the addition of P-gp and CYP3A4 inhibitors, thereby presenting hepatotoxicity adverse effect.

From the clinician's point of view, the decision to use remdesivir during the national protocol was clinically important to manage patients with severe COVID-19. Therefore, the review should take into account the management of DILI caused by remdesivir. The suggested management of using NAC for liver injury was described further through direct experience by Carothers et al.[18] NAC serves as the primary treatment for acetaminophen overdose. This mechanism has similarity to DILI caused by remdesivir, which has been described previously.[31] CYP450 pathway, which holds a significant role in producing toxic metabolites that deplete glutathione reserves after glucuronidation and sulfation pathways, was decreased by NAC through cysteine.[32] According to the guidelines from the American Association for the Study of Liver Diseases (AASLD), this treatment has potential therapeutic advantages in managing drug-induced liver injury caused by other than acetaminophen, which is the case in other reported studies. [33,34]

Many different studies have shown positive results in using NAC for treating and preventing DILI due to Non-Acetaminophen.[35] A double-blind randomized controlled trial examined the impact of NAC in 53 patients with liver injury induced by anti-tuberculosis drugs, administering 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, and 100 mg/kg over

16 hours. The study discovered that this regimen contributed to a reduced hospital stay duration,[35,36] a protocol also used by Carothers et al.[18] Updated meta-analysis emphasized that NAC administration in the management of Non-Acetaminophen Induced DILI led to greater improvements in liver function tests compared to length of stay (LOS), suggesting its potential superiority in treatment outcomes.[37]

Administering remdesivir to patients with elevated liver function tests is an added challenge for physicians, as it may further deteriorate liver condition. Close monitoring is essential, as shown in the study by Sabers et al.[19] Administration of dexamethasone may ameliorate the liver injury. In vitro co-administration of DEX significantly decreases RDV-induced cytotoxic responses in human hepatocytes, including changes in cell viability, apoptosis, DNA damage, albumin synthesis, and ALT/AST secretion.[38] The dose of dexamethasone used in the Saber et al. study was 6 mg intravenously for 7 days, which may vary greatly from other studies. This suggests a lack of data for the fixed dose and selection of corticosteroid.[19,39,40]

Despite an elevation >5 upper limit normal (ULN) of ALT, Saber et al. concluded to use remdesivir.[19] Based on consideration, the drug is not advised for patients with ALT levels ≥5 times the upper limit of normal (ULN) at baseline. In cases where ALT levels exceed 5×ULN during therapy, or the elevation is associated with liver inflammation symptoms, rising conjugated bilirubin, ALP, or INR, treatment should be discontinued. Therapy may be resumed once ALT levels drop below 5× ULN.[41] Case presented here gave clinical insight after considering the beneficial effect of remdesivir due to the patient's condition, which proved to be effective.

CONCLUSION

In conclusion, this review emphasized the potential hepatotoxic effects of remdesivir, particularly in individuals with pre-existing liver conditions, metabolic disorders, or inflammatory responses related to COVID-19. As remdesivir undergoes CYP3A4 metabolism and interacts with P-glycoprotein inhibitors, careful monitoring was essential to prevent drug-induced liver injury (DILI). Clinical evidence suggests that dexamethasone may mitigate liver toxicity, while NAC has shown effectiveness in managing non-acetaminophen-related liver damage. The absence of standardized guidelines for hepatotoxicity prevention urged the need for further study. Factors such as age-related liver function decline, comorbidities, and drug interactions should be evaluated before prescribing remdesivir. This review also emphasized the importance of continuous liver function monitoring and personalized treatment strategies to ensure safety and therapeutic outcomes in high-risk patients.

Conflict of Interest

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

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Author Contribution

The authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by ARH, and all authors commented on previous versions of the manuscript. The authors read and approved the final manuscript.

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Data Availability

All data supporting the results of this study are available from the corresponding author upon reasonable request.

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