MMSL Military Medical Science Letters Since 1925

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2024, 93(1), 10-18
ISSN 2571-113X (Online)
DOI: 10.31482/mmsl.2023.022

ORIGINAL ARTICLE

HISTOLOGICAL ASSESSMENT OF REMDESIVIR ON KIDNEY AND LIVER OF ALBINO RATS IN DIFFERENT DOSES AND THEIR WITHDRAWAL

Rana M. Ahmad ✉, Maha Al-Sammak

Department of Anatomy, College of Medicine, University of Mosul, Mosul, Iraq

Received 13th January 2023.
Accepted 12th May 2023.
Published 1st March 2024.

Summary

Background: Remdesivir has recently been used more widely as an antiviral medication, possibly due to its potency against coronavirus.
Aim: This study was aimed at detecting the toxicity of remdesivir on the liver and kidneys of albino rats at various doses, as well as the possibility of recovering to the normal structure of these tissues two weeks after drug discontinuation.
Methods: Forty adult albino rats were divided into five groups (8 rats per group). The first group was the control group; the second group received 5 mg/kg remdesivir; the third group received 10 mg/kg for five days; and the fourth and fifth groups were withdrawal groups (treated as 2nd and 3rd groups then left for two weeks). After five days of treatment, the animals of the 1st, 2nd, and 3rd groups were sacrificed, while the animals of the withdrawal groups were killed after two weeks of drug discontinuation. Both the liver and kidneys were removed and prepared for histological examination.
Results: Remdesivir-treated liver and kidneys showed histological alterations such as blood vessel congestion, mononuclear cell infiltration, and localized hepatocyte degeneration. Meanwhile, kidney sections revealed localized vacuolation of the tubular epithelium, focal glomerular tuft shrinkage with Bowman's space dilatation.
Conclusion: Remdesivir is hepatotoxic and nephrotoxic mainly, at high doses. Even after drug withdrawal, structural alterations persist, particularly at high dosages, confirming that remdesivir toxicity is dose-dependent.

Key words: Remdesivir; Remdesivir withdrawal; Histological changes

Introduction

COVID-19 (Coronavirus disease 2019) caused by severe acute respiratory distress coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, in December 2019 (1). Later on, in January 2020, the World Health Organization (WHO) declared that the SARS-CoV-2 epidemic was a public health emergency (2). COVID-19 mainly attacks the lungs, but it also attacks other organs and causes damage to these organs, such as the liver, kidneys, heart, gastrointestinal tract, and nervous system (3). The disease causes numerous clinical features as well as numerous abnormal laboratory parameters, including abnormal kidney and liver function tests (4).

✉ University of Mosul, College of Medicine, Department of Anatomy, Mosul, Iraq
rma@uomosul.edu.iq
☎ +964 772 537 8382

Remdesivir (Veklury) has been approved by the Food and Drug Administration (FDA) as an antiviral drug for the treatment of COVID-19 in children over the age of 12 and adults who require hospitalization and is administered (intravenously) using a needle in the skin (5). The drug is a nucleotide analog RNA polymerase inhibitor that was initially developed and tested for Ebola virus disease (6). As a result, remdesivir is an antiviral medicine with the ability to limit viral replication of SARS-CoV-2 (7), as it acts as a prodrug, acting as an ATP analog that competes for incorporation by viral RNA-dependent RNA polymerase and interfers with viral RNA (8). It is metabolized in the liver by CYP 3A4 and is a substrate of the hepatocyte transporters p-glycoprotein (9). The efflux rate of remdesivir out of hepatocytes may be reduced by p-glycoprotein inhibitors, resulting in a hepatocyte concentration above the toxic threshold (10).

According to the European Medicines Agency, remdesivir should not be combined with additional hepatotoxic drugs, and hepatic function should be monitored throughout treatment (11). Therefore, monitoring of liver function tests in patients receiving remdesivir is advised, as Zampino and colleagues discovered a significant increase in bilirubin, ALT, and AST levels in COVID-19 patients receiving remdesivir (12). However, it must be noted that recurrent cases of liver injury were reported in COVID-19 patients, hence, it is interesting to distinguish whether the increase in liver enzymes was attributed to remdesivir or COVID-19 (13). Therefore, if an abnormality of liver enzymes occurs after treatment with remdesivir, drug discontinuation is indicated (14). Gilead declared a laboratory abnormality as elevated liver enzymes following the use of remdesivir (15).

The elimination of remdesivir is mainly by urine and a small amount by faeces (16). Remdesivir has contraindications in patients with severe renal impairment (eGFR less than 30 mL/min) (17). As a result, monitoring of both the liver and kidneys during remdesivir treatment is required because these organs are the sites of drug metabolism and excretion. Toxicity to the liver and kidneys has been observed in numerous clinical investigations. One of these studies, conducted by Grein and his team on compassionate-use remdesivir in the treatment of COVID-19, reported that 23% of the patients had elevated liver enzymes and were forced to discontinue remdesivir in two cases, as well as acute kidney injury and hematuria in some remdesivir recipients (18). Other studies reported hepatotoxicity and nephrotoxicity as adverse effects following remdesivir therapy (19).

The present study was conducted to assess the histological changes of the liver and kidney due to the toxicity of remdesivir in Wister albino rats.

Materials and Methods

Forty healthy adult Wister albino rats weighing about 250±50 gm, male, 8-12 weeks of age, were kindly provided by the Animal House of the College of Veterinary Medicine, University of Mosul, Northern Iraq. Animal groups were placed in separate cages, under controlled temperatures (23–25 ºC), humidity (60%), and light and dark cycles of 12 hours each. The animals were fed a standard pelleted diet and water *ad libitum*. The experiment was conducted following the ethical guidelines for investigations in the laboratory (20, 21). The animals were divided into five groups (eight each) as presented in Table 1.

Table 1. The workflow of the studied groups.

	Control Group	+Remdesivir without withdrawal		+Remdesivir with withdrawal	
		5 mg/kg/day	10 mg/kg/day	5 mg/kg/day	10 mg/kg/day
Group ID	G1	G2	G3	G4	G5

Group 1 (control group): a plain group that contains eight animals.
Group 2: (n=8) treated with 5 mg/kg remdesivir body weight daily for five days.
Group 3: (n=8) treated with 10 mg/kg remdesivir body weight for five days.
Group 4: (n=8) treated as group 2 and then left for two weeks as the withdrawal group.
Group 5: (n=8) treated as group 3 then left for two weeks as the withdrawal group.

All animals were injected intraperitoneally (IP) with remdesivir, which was obtained from the local markets in Iraq. Gilead Sciences Inc. provided the VEKLURY® (remdesivir) of 100 mg/20 ml (5 mg/ml) Ampule, which was given without dilution at doses of 0.25 ml for group 2 animals and 0.5 ml for group 3 animals. On the 5th day

of the experiment, the animals in groups 1, 2, and 3 were sacrificed, while those in groups 4 and 5 were left for another two weeks. After that, their liver and kidney tissues were removed and rinsed in the sink before being transferred to a Petri dish containing normal saline solution, dried on filter papers, divided into pieces of 1 cm^3 × 1 cm^3 and preserved in 10% buffered formalin. Tissue processing, sectioning, and staining were done following the procedure of Suvrana (2013). The tissue was dehydrated with ascending grades of alcohol and cleared with xylene (3 changes per hour). Then, it was impregnated into 3 changes of paraffin wax with 56-60 °C melting paraffin (each change for 1 hr). The tissue was embedded in fresh paraffin wax to obtain a solid block, which was prepared for sectioning into 4-5 µm thick sections by using a Reichart rotary microtome. Deparaffinization was achieved with two changes of xylene (each lasting 5 minutes) and carried out at the staining time. Rehydration was achieved with descending grades of alcohol, and then the sections were transferred into tap water for 2 min before staining with hematoxylin and eosin.

Results

The animals in all groups during the experiment were active with good and normal food intake. When the first group (control group) was viewed under the microscope, liver sections showed normal cords of polygonal hepatocytes around the central vein, with the normal portal area containing a hepatic artery, portal vein, and bile canaliculi (Figure 1A). The kidney sections also revealed normal proximal convoluted tubules (PCT), distal convoluted tubules (DCT), and normal renal corpuscles composed of glomeruli tufts surrounded by Bowman's space (Figure 1B).

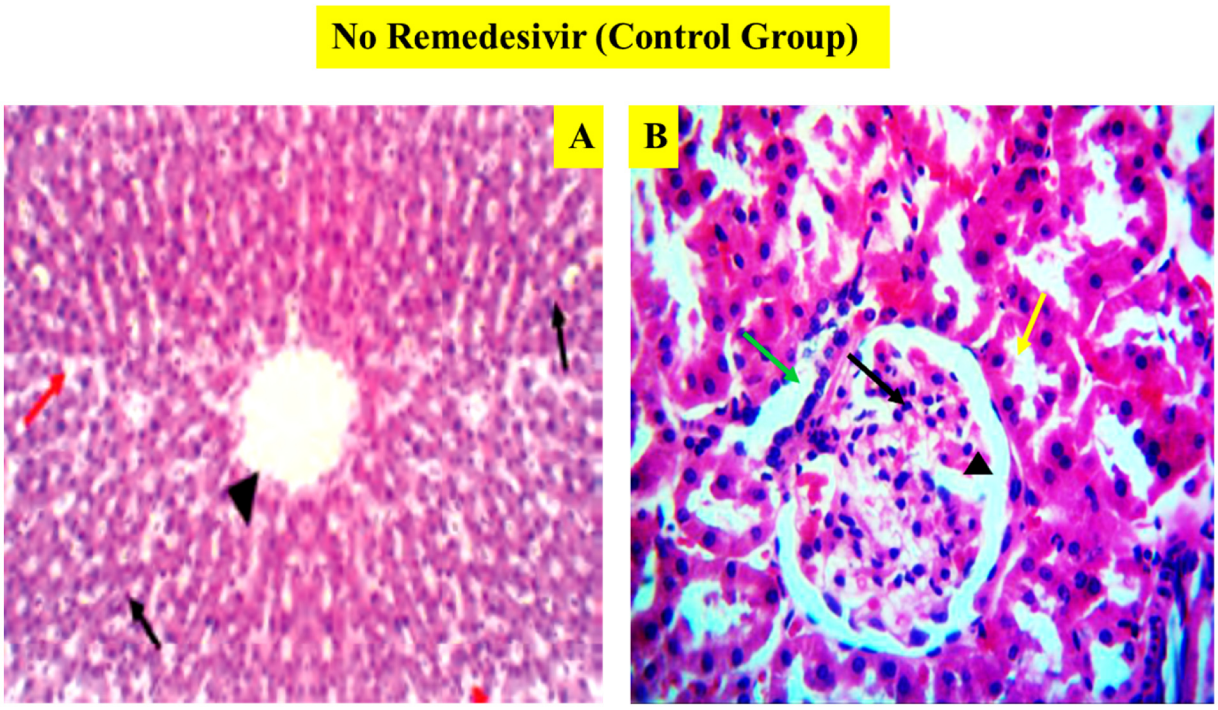

Figure 1. A representative image for the control group treated with remdesivir-free distilled water. (A) Liver showing the normal structure, central vein (arrowhead) hepatocytic plates (black arrows), and sinusoids (red arrows). (B) Kidney showing glomerulus (black arrow), bowman's space (arrowhead), PCT (yellow arrow), and DCT (green arrow). (A: H & E X100) (B: H & E X 400).

In the second group, liver sections revealed preserved liver architecture, mild congestion of blood vessels, mononuclear cell infiltration in the portal area, and a focal area of degeneration of hepatocytes (Figure 2A). Meanwhile, kidney sections showed preserved kidney architecture, focal shrinkage of the glomerular tuft with Bowman's space dilatation and congestion of glomerular capillaries, and a localized area of vacuolar degeneration of the tubular lining epithelium (Figure 2C).

The liver in the third group showed more severe changes, including coagulative necrosis of hepatocytes around the central vein, infiltration of inflammatory cells within the liver parenchyma, and ductular reaction in the portal area, including hyperplasia of bile canaliculi (Figure 2B). Kidney sections on the other hand depicted more pronounced changes, including shrinkage of the glomerular tuft with more congestion of glomerular capillaries, in addition to vacuolar degeneration of renal tubular lining epithelium (Figure 2D).

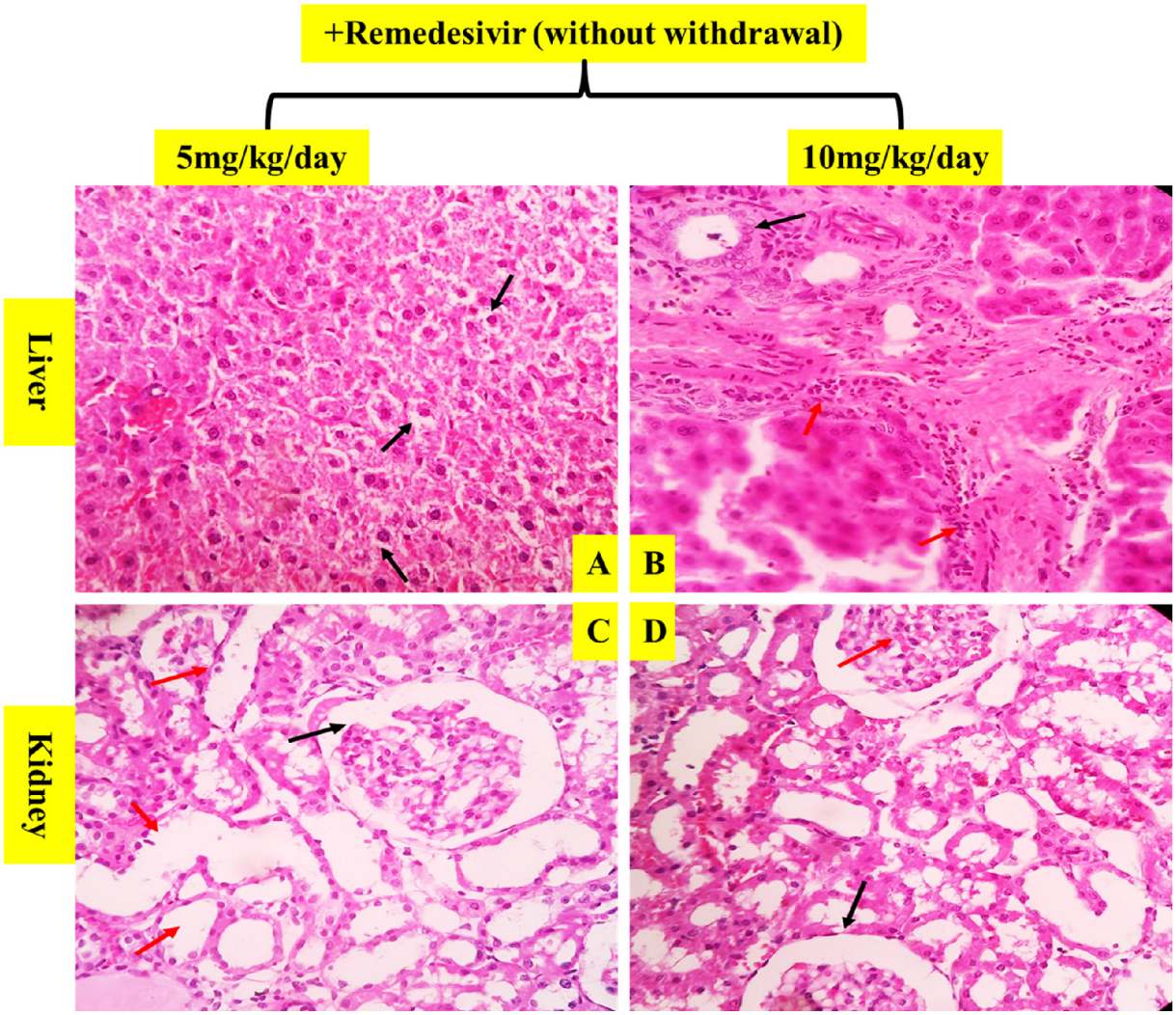

Figure 2. A representative image for the remedesivir treated group. (A) section of the rat's liver showed a focal area of vacuolar degeneration of hepatocytes (black arrows) (B) section of the rat's liver showed infiltration of inflammatory cells around the portal area (red arrows) and hyperplasia of bile canaliculi (black arrow). (C) section of the rat's kidney showed congestion of glomerular capillaries (black arrow) and vacuolar degeneration of tubular lining epithelium (red arrows) (D) section of rat's kidney showed shrinkage of glomerular tuft with bowman's space dilatation (black arrow) and more congestion of glomerular capillaries (red arrow) (A: H & E X400) (B: H & E X 400) (C: H & E X400) (D: H & E X 400).

In the fourth group, the liver showed no congestion, and a regression in the inflammatory cell infiltration with mild vacuolar degeneration of the hepatocytes as observed in Figure 3A. Meanwhile, kidney sections also showed improvement in their general architecture, with no congestion and no vacuolar degeneration of the tubular lining epithelium (Figure 3C).

Figure 3D highlights liver sections in the fifth group. It was observed that there was congestion but that it was less prominent than previous changes observed in the third group with less inflammatory cell infiltration and ductal

hyperplasia (Figure 3B). In the kidney sections, fewer changes were observed compared to the third group, as reduced congestion, vacuolation, and glomeruli returned to normal.

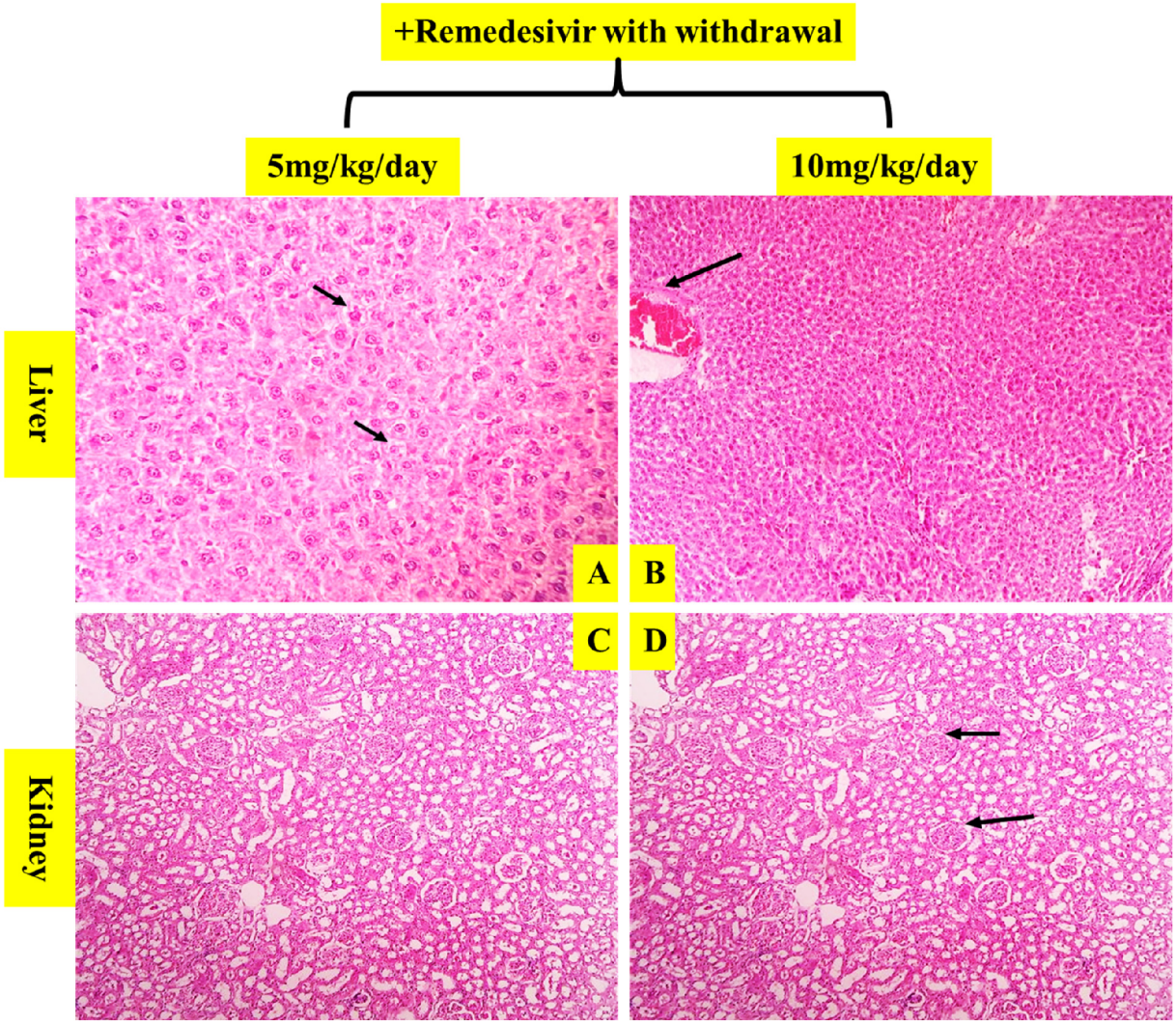

Figure 3. A representative image for the remedesivir treated group. (A) section of the rat's liver showed improvement except for mild vacuolar degeneration of hepatocytes (black arrows). (B) section of the rat's liver showed a mild degree of improvement as less congestion (black arrow), less inflammatory cell infiltration, and ductal changes. (C) section of the rat's kidney showed improvement in the general architecture of the kidney. (D) section of the rat's kidney showed mild improvement as less congestion and less vacuolar degeneration of renal tubular lining epithelium with reversibility of glomeruli (black arrow) (A: H & E X400) (B: H & E X 100) (C: H & E X 100) (D: H & E X 100).

Discussion

There are liver and kidney injuries in remdesivir-treated animals, as an acute liver injury was observed due to hepatic ischemia associated with cytokine storm syndrome and hypoxia in COVID-19 patients (23). It was also observed that in COVID-19, a coronavirus infection that causes severe acute respiratory syndrome, causes liver damage (24). Apart from the study conducted by Van *et al*., which found that repeated toxic remdesivir in the animal led to increased renal toxicity, there are few studies on the histological effects of remdesivir on the liver and kidneys similar to the current study. A dose-dependent kidney injury and/or impaired function, which was supported

by histopathological findings of renal tubular atrophy, casts, and basophilia was reported (25). El-Haroun and colleagues conducted more recent studies in which they employed a higher dose of remdesivir. They discovered more serious changes, such as significant disruption of the histology of the renal cortex, where the glomeruli appeared to be swollen, fragmented, and degenerating. Also, a significant widening of Bowman's space with dilated renal tubules and an acidophilic cast in their lumen, combined with degeneration of the renal interstitium, left wide spaces in between renal tubules. These observations conform with the changes that are dose-related (26). Another investigation in rhesus monkeys found remdesivir-induced renal impairment at dosages of 5, 10, and 20 mg/kg per day for 7 days (27). There are many biochemical studies on felids, research done by Wang and his colleagues on patients treated with remdesivir indicated that 12 of these patients had elevated liver enzymes and the other 7 had renal impairment (8). In another case study, an obese patient developed abrupt hepatic failure after receiving remdesivir therapy (28). Some studies, on the other hand, found no significant differences in liver and renal function tests from the baseline (29, 30).

Remdesivir is a nucleotide analog RNA polymerase inhibitor that has shown efficacy in the treatment of COVID-19, but its safety has not been proven in this study. Remdesivir was used for 5 days at a concentration of 10 mg/kg, which is toxic to the liver and kidneys, and this toxicity is dose-dependent even if the drug is stopped two weeks later. To the best of our knowledge, this study is the first to report this observation, which has not been addressed by other authors. As a result, many COVID-19 mortalities may occur as a result of the drug's complications on the kidneys and liver, particularly in those with impairment. It is, therefore, critical to monitor liver and kidney functions and evaluate the hepatic and kidney safety of remdesivir administration to COVID-19 patients (12).

Damage to the liver and kidney tissues caused by free radicals due to the toxic effect of remdesivir has been reported by other researchers (24). Remdesivir causes acute nephrotoxicity and hepatotoxicity due to the direct inflammatory effect of cytokines following COVID-19. The drug causes a decreased glomerular filtration rate and elevates liver enzymes, causing damage to kidney and liver tissues, similar to other studies (31). Remdesivir causes mitochondrial toxicity and injury in the renal tubular epithelial cells and hepatocytes, leading to the accumulation of free radicals and oxidative damage, which lead to necrosis and degeneration of hepatic and renal tissues (24). Liver and kidney toxicity may be due to the destruction of the lysosomal membrane caused by remdesivir leading to the liberation of their hydrolytic enzymes, which promote death and lysis of the cells (32). In the present study, distortion in the histological structure of the liver and kidneys could be due to the intermediate substances secreted by inflammatory cells, causing vasodilation and congestion of blood vessels (33).

Remdesivir is a broad-range antiviral drug used primarily for the treatment of hepatitis C and is now used for the treatment of coronavirus (34, 35). The effect of remdesivir on the histological structure of the liver and kidneys is dose-dependent and this may be due to the generation of free radicals by the drug leading to damage and degeneration of renal and liver cells (36). Remdesivir crosses the blood-brain barrier in very small amounts. It is rapidly absorbed into the tissue after entering the cells by intracellular hydrolase and is converted to active metabolites of nucleotide triphosphate in the cells causing a rate of damage and necrosis. This observation is in agreement with other studies, which found remdesivir to be very toxic to tissue cells (36).

In both withdrawal groups (4th and 5th groups), there was an improvement from their treated groups (2nd and 3rd groups), but the changes are still present in the 5th group. This indicates that remdesivir toxicity is dose-dependent even if the drug is discontinued after two weeks. The variation in response could be attributed to several factors, including the impact of the surrounding endogenous milieu on responsiveness to the maintenance of subcellular quasi-equilibrium (37-40), implying that a cytokine storm could alter the disease profile, illness, or body response to remdesivir. The limitations of the present study include the use of only two doses, the fact that the study is primarily qualitative rather than quantitative, and the fact that the results were obtained using only histological techniques.

Conclusion

This study revealed that remdesivir is toxic to the liver and kidneys and that its toxicity is dose-dependent. The liver and kidney tissues do not recover to their normal architecture and histology during withdrawal from this drug. Therefore, when administering remdesivir to patients, especially those with hepatic and renal impairment, it is important to monitor their liver and kidney function tests.

Acknowledgments

We would like to express our appreciation and gratitude to the College of Medicine and the College of Veterinary Medicine at the University of Mosul for their support of this study.

Funding

Self-funded.

Conflict of interest

The authors declare no conflict of interest concerning the present study.

Adherence to Ethical Standards

The study was approved by the Medical Research Ethics Committee in the College of Medicine, University of Mosul with approval number (UoM/COM/MREC/21-22(6)) on April 10, 2021.

References

1. Prajapat M, Sarma P, Shekhar N, et al. Update on the target structures of SARS-CoV-2: A systematic review. Indian Journal of Pharmacology. 2020;52(2):142. https://doi.org/10.4103/ijp.IJP_338_20.
2. Darweesh O, Abdulrazzaq GM, Al-Zidan RN, et al. Evaluation of the Pharmacologic Treatment of COVID-19 Pandemic in Iraq. Current Pharmacology Reports. 2021;7(4):171-178. https://doi.org/10.1007/s40495-021-00262-9
3. Zhang Y, Geng X, Tan Y, et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomedicine & pharmacotherapy. 2020;127:110195. https://doi.org/10.1016/j.biopha.2020.110195
4. Paranjpe I, Russak AJ, De Freitas JK, et al. Clinical characteristics of hospitalized COVID-19 patients in New York City. MedRxiv. 2020. https://doi.org/10.1136/bmjopen-2020-040736
5. Matos RI, Chung KK. DoD COVID-19 practice management guide: clinical management of COVID-19. Defense Health Agency Falls Church United States; 2020 Jun 18.
6. Chan KW, Wong VT, Tang SCW. COVID-19: an update on theepidemiological, clinical, preventive and therapeutic evidence and guidelines of integrative Chinese-western medicine for the management of 2019 novel coronavirus disease. Am J Chin Med. 2020;13:1–26. https ://doi.org/10.1142/S0192 415X2 05003 78.
7. Ansems K, Grundeis F, Dahms K, et al. Remdesivir for the treatment of COVID-19. Cochrane Database of Systematic Reviews. 2021(8). https://doi.org/10.1002/14651858.CD014962
8. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The lancet. 2020;395(10236):1569-1578.
9. Arundel C, Lewis JH. Drug-induced liver disease in 2006. Current opinion in gastroenterology. 2007;23(3):244-254.
10. Leegwater E, Strik A, Wilms EB, et al. Drug-induced liver injury in a patient with coronavirus disease 2019: Potential interaction of remdesivir with P-Glycoprotein inhibitors. Clinical Infectious Diseases. 2021;72(7):1256-1258. https://doi.org/10.1093/cid/ciaa883
11. Dale AP, Hudson MJ, Cullen T, et al. Administration of bamlanivimab to skilled nursing facility residents during a COVID-19 outbreak, January-February 2021, Arizona. Journal of the American Medical Directors Association. 2021;22(7):1357-1358. https://doi.org/10.1016/j.jamda.2021.04.023
12. Zampino R, Mele F, Florio LL, et al. Liver injury in remdesivir-treated COVID-19 patients. Hepatol Int. 2020;1-3. https://doi.org/10.1007/s12072-020- 10077-3.
13. Li J, Fan JG. Characteristics and mechanism of liver injury in 2019 coronavirus disease. Journal of Clinical and Translational Hepatology. 2020;8(1):13. https://doi.org/10.14218/JCTH.2020.00019
14. Fan Q, Zhang B, Ma J, et al. Safety profile of the antiviral drug remdesivir: An update. Biomedicine & Pharmacotherapy. 2020;130:110532. https://doi.org/10.1016/j.biopha.2020.110532
15. Ison MG, Wolfe C, Boucher HW. Emergency use authorization of remdesivir: the need for a transparent distribution process. Jama. 2020;323(23):2365-2366. https://doi.org/10.1001/jama.2020.8863

16. Yang K. What do we know about remdesivir drug interactions?. Clinical and translational science. 2020;13(5):842. https://doi.org/10.1111/cts.12815
17. Stella VJ, Rajewski RA. Sulfobutylether-β-cyclodextrin. Int J Pharm. 2020;583:119396. https://doi.org/10.1016/j. ijpharm.2020.119396.
18. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. New England Journal of Medicine. 2020;382(24):2327-2336. https://doi.org/10.1056/NEJMoa2007016.
19. Wong CK, Au IC, Cheng WY, et al. Remdesivir use and risks of acute kidney injury and acute liver injury among patients hospitalised with COVID-19: A self-controlled case series study. Alimentary Pharmacology & Therapeutics. 2022. https://doi.org/10.1111/apt.16894.
20. Abdulqader SW, Faisal IM, Saeed MG, et al. Fluvoxamine Provide a Gastro-Protection Against Vitiated Insult. Indian Journal of Forensic Medicine & Toxicology. 2022;16(1):1047. https://doi.org/10.37506/ijfmt.v16i1.17633
21. Abdulqader SW, Faisal IM, Saeed MG, et al. Fluvoxamine Suppressed Oxidative Stress associated with Tissue Erosion. Research Journal of Pharmacy and Technology. 2022;15(2):819-824. https://doi.org/10.52711/0974-360X.2022.00136.
22. Suvarna SK, Layton C, Bancroft JD, John D (2013). Bancroft's Theory and Practice of Histological Techniques. 7th ed., Churchill Livingstone, Elsevier Limited ,UK, pp:215-236.
23. McGrowder DA, Miller F, Anderson Cross M, et al. Abnormal liver biochemistry tests and acute liver injury in COVID-19 patients: current evidence and potential pathogenesis. Diseases. 2021;9(3):50. https://doi.org/10.20944/preprints 20210.0552.
24. Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver international. 2020;40(5):998-1004. https://doi.org/10.1111/liv.14435.
25. van Laar SA, de Boer MG, Gombert-Handoko KB, et al. LUMC-COVID-19 Research Group. Liver and kidney function in patients with COVID-19 treated with remdesivir. British journal of clinical pharmacology. 2021;87(11):4450-4454. https://doi.org/10.1111/bcp.14831.
26. Hala El-Haroun , Manar Ali Bashandy, Mona Soliman. Impact of Remdesivir on the kidney and Potential Protective Capacity of Granulocyte-Colony Stimulating Factor Versus Bone Marrow Mesenchymal Stem Cells in Adult Male Albino Rats. Egyptian journal of Histology. 2022;45(2):338-358. https://doi.org/10.21608/ejh.2021.60527.1426.
27. Lo MK, Feldmann F, Gary JM, et al. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. Science translational medicine. 2019;11(494): eaau9242. https://doi.org/10.1126/scitranslmed.aau9242
28. Kevin L, Valerie G, Michael P, et al. Acute Liver Failure Secondary to Remdesivir in the Treatment of COVID-19. ACG Case Reports Journal. 2022; 9(10):p e00866. https://doi.org/10.14309/crj.0000000000000866
29. Wang S, Huynh Ch, D'Andrea Joseph D. Assessment of Safety of Remdesivir in Covid – 19 Patients with Estimated Glomerular Filtration Rate (eGFR) < 30 ml/min per 1.73 m^2. Journal of Intensive Care Medicine. 2021;37(6). https://doi.org/10.1177/08850666211070521.
30. Nasir H, Raja KM, Satti Sh, et al. Safety of Remdesivir in Covid Patients with Acute or Chronic Kidney Disease. Ann Pak Inst Med Sci. 2022;18(4):300-303. https://doi.org/10.48036/apims.v18i4.668.
31. Goldman JD, Lye DC, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. New England Journal of Medicine. 2020;383(19):1827-1837. https://doi.org/10.1056/NEJMoa2015301.
32. Korovila I, Höhn A, Jung T, et al. Reduced liver autophagy in high-fat diet induced liver steatosis in New Zealand obese mice. Antioxidants. 2021;10(4):501. http://doi.org/10.3390/antiox 10040501.
33. Sharma DJ, Deb A, Sarma P, et al. Comparative Safety and Efficacy of Remdesivir Versus Remdesivir Plus Convalescent Plasma Therapy (CPT) and the Effect of Timing of Initiation of Remdesivir in COVID-19 Patients: An Observational Study From North East India. Cureus. 2021;13(11). https://doi.org/10.7759/cureus.19976.
34. Sharm Harkars. Overiew on Remdesivir international Journal of Science and Research, 2021;10(6). https://doi.org/1/10.21275/MR 21620233.
35. Piscoya A, Ng-Sueng LF, Parra del Riego A, et al. Efficacy and harms of remdesivir for the treatment of COVID-19: A systematic review and meta-analysis. PloS one. 2020;15(12):e0243705. https://doi.org/10.1371/journal.pone.0243705
36. Rahimi MM, Jahantabi E, Lotfi B, et al. Renal and liver injury following the treatment of COVID-19 by remdesivir. Journal of Nephropathology. 2021;10(2):1-4. https://doi.org/10.34172/jnp.2021.10
37. Shephard MT, Merkhan MM, Forsyth NR. Human Mesenchymal Stem Cell Secretome Driven T Cell Immunomodulation Is IL-10 Dependent. International Journal of Molecular Sciences. 2022;23(21):13596. https://doi.org/10.3390/ijms232113596

38. Narayanasamy KK, Price JC, Merkhan M, et al. Cytotoxic effect of PEI-coated magnetic nanoparticles on the regulation of cellular focal adhesions and actin stress fibres. Materialia. 2020;13:100848. https://doi.org/10.1016/j.mtla.2020.100848
39. Merkhan MM, Shephard MT, Forsyth NR. Physoxia alters human mesenchymal stem cell secretome. Journal of Tissue Engineering. 2021;12:20417314211056132. https://doi.org/10.1177/20417314211056132.
40. Forsyth NR, Steeg R, Ahmad M, et al. Mimicking Physiological Oxygen in Cell Cultures. InCell Culture Technology 2018 (pp. 129-137). Springer, Cham. https://doi.org/10.1007/978-3-319-74854-2_8.