

Appropriately Designed Studies are required to assess the AED Profile of Remdesivir

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LETTER TO THE EDITOR

We read with interest the article by Kang, *et al.* on a retrospective, national, multicenter study on the adverse events (AED) of remdesivir in 2416 patients with SARS-CoV-2 infection (SC2I), collected during an observational period of one year (January to December 2021) [Kang, H. *et al.*, 2023]. It was found that 66.2% of patients experienced at least one AED and 13.8% experienced at least one severe AED [Kang, H. *et al.*, 2023]. The incidence of AEDs was not increased in patients with SC2I receiving remdesivir compared to controls, but the AED incidence was increased in patients with renal insufficiency [Kang, H. *et al.*, 2023]. The most common severe AEDs in this group were anaemia, hypokalemia, and thrombocytopenia [Kang, H. *et al.*, 2023]. It was concluded that remdesivir should be administered with caution in patients with renal insufficiency [Kang, H. *et al.*, 2023]. The study is impressive, but some points require discussion.

The first limitation is that comedications were not registered and not included in the assessment [Kang, H. *et al.*, 2023]. The pharmacokinetics and pharmacodynamics of remdesivir may be highly dependent on comedications as some of them can be metabolised in the liver by the same pathways as remdesivir, thereby increasing or decreasing serum remdesivir levels. Interactions between remdesivir and any other drugs that the enrolled patients were taking for the treatment of SC2I must be considered as potential influencing factors on pharmacokinetics and dynamics of remdesivir.

A second limitation is that comorbidities other than renal insufficiency and hepatopathy were not included in the assessment [Kang, H. *et al.*, 2023]. Knowledge of comorbidities is crucial as they can have a strong influence on the pharmacodynamics and pharmacokinetics of a drug. These include in particular diseases such as heart failure, thyroid dysfunction, pituitary disease, or adrenal gland dysfunction.

A third limitation is that the number of patients vaccinated against SARS-CoV-2 was not reported. Vaccinated patients may experience a different course of disease than of unvaccinated patients and may therefore require remdesivir for a different period and at a different dosage.

A fourth limitation is that the dosage of remdesivir each patient received and the duration of use were not included in the assessment.

A fifth limitation is that the severity of SC2I was not reported [Kang, H. *et al.*, 2023]. It is crucial to know the severity of SC2I because people with mild SC2I may respond differentially to remdesivir than people with severe SC2I.

It is not comprehensible why only hepatotoxicity, nephrotoxicity, electrolyte abnormalities, anemia, thrombocytopenia, and allergic reactions were classified as AEDs [Kang, H. *et al.*, 2023]. Other side effects of remdesivir that were not included in the study include back pain, chest tightness, chills, cough, dark-coloured urine, dysphagia, tachycardia, fever, flushing, headache, hives, itching, light-coloured stools, nausea, vomiting, swelling of the eyelids, face, lips, or tongue, stomach pain, persistent difficulty breathing, unusual tiredness or weakness, yellow eyes or skin, seizures, or skin rash [www.mayoclinic.org].

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Whether or not remdesivir causes AEDs in patients with SC2I depends not only on renal and liver function, but also on several other factors such as age, dosage, duration of use, comedication, comorbidities, and severity of SC2I.

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Compliance with Ethics Guidelines: This article is based on previously conducted studies and does

not contain any new studies with human participants or animals performed by any of the authors.

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