Prediction of remdesivir resistance in COVID-19 illness: Need for development of clinical laboratory test

Deepak Kumar¹ · Sukhpreet Singh¹ · Deepak Yadav¹ · Sumanpreet Kaur¹ ·
Monu Kumari¹ · Samiksha Jain¹ · Rajasri Bhattacharyya¹ · Dibyajyoti Banerjee¹

Received: 22 April 2021 / Accepted: 3 June 2021 / Published online: 10 June 2021
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Keywords COVID-19 · Remdesivir · Resistance · RNA dependent RNA polymerase (RdRp)

Dear Editor,

Remdesivir is thought to be effective for certain groups of patients suffering from COVID-19 illness. Currently, FDA has approved it for the purpose and WHO has issued a conditional recommendation for its use. Some evidence has been gathered in favor of its use, but data from large scale clinical trials are expected to give more insight into the matter [1].

At the present moment, molecular understanding regarding the use of remdesivir in SARS-CoV2 infected patients (COVID-19 disease) is scanty. Remdesivir is a nucleotide analogue that inhibits RNA dependent RNA polymerase (RdRp) of the virus. In case the binding site of the drug is mutated, remdesivir may not fit in the active site for the desired effect. It is in this context, we have docked remdesivir at the binding site of wild type RdRp bound

template primer RNA complex (please see supplementary). The remdesivir was observed to fitted there with binding energy -8.68 kcal/mol. The reported interacting residues (R555, V557, D618, T680, N691, D760 and D761) are in contact with remdesivir ring and are shown in Fig. 1a [2]. The nucleoside homolog ring faces towards the primer-template implying inhibition of elongation of viral RNA.

The most negative binding energy obtained in mutant cases (R555, V557, D618, T680, N691, D760, D761) were -8.93, -8.42, -6.55, -7.65, -7.42, -8.70, -8.26, respectively. In the mutant cases, remdesivir binding is shifted from the actual elongation site. However, in R555A and D760A mutant cases, the binding energy was observed to be more negative (8.93 and 8.70 kcal/mol, respectively). In Fig. 1b, remdesivir binding with D760 mutant RdRp with template primer is shown.

We have observed that if any of the above-mentioned interacting residues are mutated, then remdesivir binding position is changed. So, in case of mutated RdRp, remdesivir may not stop the viral RNA elongation and the virus may acquire drug resistance. In SARS-CoV2 virus, mutation near the binding sites (putative docking site of remdesivir in RdRp) is found [3]. However, it causes remdesivir resistance or not is currently unknown [4]. There are views that the remdesivir resistant strain cannot survive [5]. We believe that at the current moment it is impossible to comment with certainty that remdesivir resistant strain will cause a fatal COVID-19 disease or not and more focussed research should be dedicated in the concerned field. For stepping towards such direction, we must amplify the critical viral regions and sequence it for understanding the emergence of remdesivir resistant SARS-CoV2 strain.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12291-021-00987-w>.

✉ Rajasri Bhattacharyya
bdr.rajassri@yahoo.in

✉ Dibyajyoti Banerjee
dibyajyoti5200@yahoo.co.in

¹ Department of Experimental Medicine and Biotechnology,
Postgraduate Institute of Medical Education and Research,
Chandigarh 160012, India

Fig. 1 Conformation of remdesivir in wild type (WT) and D760 mutant RdRp-DNA complex are shown. In (a), the residues of RdRp interacting with remdesivir are represented. In (b), the position of

remdesivir (in cyan colour and designated as Mutant) in D760 mutant RdRp is shown. The actual position of remdesivir is represented in magenta colour and noted as WT

Author's contribution DK has done the work under supervision of RB. SS and SK check the in-silico part of the work. All the other authors have helped to develop the concept, criticize the data and approved the final version of the manuscript.

Funding SS acknowledges University Grant Commission, India, for providing fellowship [F.No. 16–6(Dec.2017)/2018(NET/CSIR)]. SK [File No:09/141(0228)/2020-EMR-I] and MK [File No: 09/141(0217)/2019-EMR-I] acknowledges Council for Scientific and Industrial Research, New Delhi, India, for providing financial assistance in the form of fellowship. DK, DY, SJ, RB and DB acknowledge the Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Data Availability The raw data is in the custody of the authors.

Declarations

Conflict of interest None.

Consent for Publication All the authors have approved the final version of the manuscript.

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