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Letter to Editor

Pulmonary administration of remdesivir in the treatment of COVID-19

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We read, with great interest, the commentary "Remdesivir for Treatment of COVID-19: Combination of Pulmonary and IV Administration May Offer Additional Benefit" by Sun [1]. In this commentary, Sun [1] suggests that intravenous administration of remdesivir is unlikely to produce sufficiently high concentrations of its active antiviral agent, the nucleoside triphosphate (Nuc-TP), in human lungs to effectively eliminate SARS-CoV-2. This led Sun [1] to propose investigations into pulmonary delivery of remdesivir, modifications of its prodrug moiety, and use of nanoformulations of this agent to improve treatment of COVID-19 pneumonia. We consider that these issues are highly relevant but are uncertain about the conclusion that intravenous administration of remdesivir in the treatment of COVID-19 is unlikely to produce therapeutically effective concentrations of this prodrug and its active antiviral agent in human lungs.

First, results from *in vitro* assays for assessment of the activity of antiviral agents vary substantially being highly dependent on viral quantification method, viral isolate, and cell type used for viral propagation [2, 3]. Sun [1] retrieved 50% and 90% maximal inhibitory concentrations (IC_{50} and IC_{90}) of 0.77 and 1.76 μM, respectively, for the anti-SARS-CoV-2 activity of remdesivir in Vero E6 African green monkey kidney cells from a study by Wang *et al.* [4]. Assuming a 10-fold intracellular accumulation of Nuc-TP relative to extracellular remdesivir, these inhibitory values were used to derive the intracellular Nuc-TP IC_{50} and IC_{90} values of 7.7 and 17.6 μM, which were compared with an estimated intracellular Nuc-TP concentration in the range of 4 to 10 μM in human lungs [1]. However, other studies have reported IC_{50} and IC_{90} values for the anti-SARS-CoV-2 activity of remdesivir that differed from those adopted by Sun. This includes the study by Pruijssers *et al.* [5] that reported IC_{50} values of 0.001 and 0.009 μM in primary human airway epithelial (HAE) cells in two independent experiments, whereas a higher IC_{50} value of 0.28 μM and an IC_{90} value of 2.48 μM were observed with Calu-3 2B4 respiratory epithelial cells. Pruijssers *et al.* [5] also found that remdesivir inhibited SARS-CoV-2 with IC_{50} and IC_{90} values of 1.65 and 2.40 μM, respectively, in Vero E6 cells, which are highly permissive to SARS-CoV-2 and therefore commonly used to study this virus [6, 7]. Moreover, an IC_{50} value of 0.38 μM has been reported for the anti-SARS-CoV-2 activity of remdesivir in Caco-2 colorectal adenocarcinoma cells [8]. The differences in *in vitro* antiviral activity of remdesivir between different cell types may partially reflect differences in the ability to convert this prodrug to its antiviral active agent with the Vero E6 cell line apparently activating remdesivir less efficiently than other types of cells [5]. Hence, this cell line, and probably other Vero cell lines as well, may be less suitable for studies of the intracellular pharmacology of remdesivir. Assuming that Nuc-TP in general accumulates 10-fold intracellularly relative to extracellular remdesivir, the estimated intracellular IC_{50} values of Nuc-TP in the above cells would all fall below the intracellular Nuc-TP concentration range of 4 to 10 μM in human lungs except for those found using Vero E6 cells. Importantly, the primary HAE cells, in which markedly low IC_{50} values were produced, may represent a biologically more appropriate *in vitro* model than established cell lines such as Vero E6. Taken together, the intracellular IC_{50} and IC_{90} values of the Nuc-TP in human lungs estimated by Sun [1] appear excessively high as they were based on findings done using the Vero E6 cell line.

Second, the achievable maximum plasma concentration (C_{max}) of remdesivir administered intravenously at an approved dose has been reported to exceed two out of four IC_{50} values and two out of three IC_{90} values determined for this prodrug [3]. These IC_{50} and IC_{90} values had all been estimated using Vero cell lines for propagation of SARS-CoV-2. Accordingly, comparison of C_{max} of remdesivir with the IC_{50} values for its anti-SARS-CoV-2 activity in primary HAE cell cultures would have produced markedly higher C_{max}/IC_{50} ratios and suggested that this prodrug effectively eliminates SARS-CoV-2 in human lungs at approved intravenous doses.

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In brief, the most recent data, which may not all have been available to Sun [1] at the time of the submission of his commentary, do not convincingly support the notion that intravenous administration of remdesivir is unable to produce sufficiently high local concentrations of the active antiviral agent of this prodrug to eliminate SARS-CoV-2 from the lungs in COVID-19 pneumonia. However, this does not exclude that there is a marked potential for improvement of the clinical outcome of COVID-19 pneumonia by combining intravenous and pulmonary administration of remdesivir or by other approaches such as redesign of the remdesivir prodrug moiety and use of nanoformulated drug delivery.

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