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Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU—authors' response

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Sir,

We welcome the important comments raised by Bonazzetti *et al.*[1] on our recent article concerning the use of remdesivir in patients with COVID-19 undergoing mechanical ventilation.[2]

Bonazzetti *et al.*[1] suggest that our study does not appropriately consider immortal time bias, which could lead to a misinterpretation of the results.

In this regard, the median time delay between treatment initiation and admission to the ICU was 7 days (IQR = 4–8 days). This delay was due to the time interval between the request of remdesivir as compassionate use and its actual delivery. In our retrospective study, only one patient died before the delivery of the drug. Although this patient was not actually counted in the remdesivir group, the survival time considered in this study started from the day of admission to the ICU and not from the initiation of remdesivir, according to an intention-to-treat approach. In light of these considerations, although the immortal time bias could potentially overestimate the survival rate of the remdesivir group, underestimation of the survival rate in the remdesivir group could arise from the delay in drug treatment.

An additional observation raised by Bonazzetti *et al.*[1] concerns the inclusion of the SOFA score in our multivariate analysis. SOFA score was excluded as our univariate analysis showed no significant relationship with the survival rate ($P = 0.488$). Indeed, at the time of admission in the ICU, patients were mostly characterized by respiratory failure with no other organ dysfunctions.

As extensively explained in the discussion of the manuscript, our study presents biases mainly related to the selection of patients included in the treatment group. Immortal time bias has marginal to no impact on the estimated survival rate reported in our study. Our work remains an example of the use of remdesivir in an extremely difficult context in which mortality in intensive care was much higher than that today and available treatments were limited.

Despite all these limitations, we believe that retrospective studies retain their importance given that the efficacy of remdesivir in the treatment of SARS-CoV-2 infections remains uncertain after the publication of several trials showing conflicting results.[3–6]

Transparency declarations

None to declare.

References

1 Bonazzetti C, Milazzo L, Giacomelli A *et al.* Comment on: Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU. *J Antimicrob Chemother* 2021; doi:10.1093/jac/dkab033.

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6 WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19—interim WHO Solidarity trial results. *New Engl J Med* 2021; **384**: 497–511.