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# Remdesivir, on the road to DisCoVeRy

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Despite the availability of effective SARS-CoV-2 vaccines, improving care for patients with symptomatic infection remains relevant. Strategies to blunt the hyperinflammatory state that characterises severe COVID-19 include broad-spectrum immunosuppressive drugs such as corticosteroids, targeted immunomodulatory treatments such as tocilizumab or baricitinib, and direct-acting antivirals to reduce viral load.

In *The Lancet Infectious Diseases*, Florence Ader and colleagues[1] report results of the DisCoVeRy trial, the fifth large, randomised, controlled trial with the broad-spectrum antiviral drug remdesivir.[1] In this open-label study, 857 patients admitted to hospital with severe COVID-19 (oxygen saturation $SpO_2$ ≤94% or in need of supplemental oxygen or respiratory support) were randomly assigned to remdesivir plus standard of care or standard of care alone. There was no significant difference in the primary outcome, the odds of better clinical status defined on the WHO ordinal scale, at day 15 (odds ratio 0·98 [95% CI 0·77–1·25]; p=0·85). This finding remained consistent across all prespecified subgroup analyses, including duration of symptoms before admission or disease severity at random assignment. There was also no significant difference in 28-day mortality (0·93 [0·57–1·52]; p=0·77), and none of the time-to-improvement analyses showed any significant benefit in favour of remdesivir. However, in an exploratory subgroup analysis of patients without mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at random assignment, the hazard for the composite endpoint of new mechanical ventilation, ECMO, or death was lower in the remdesivir group than in the standard-of-care group (hazard ratio [HR] 0·66 [95% CI 0·47–0·91]; p=0·010).

How do these findings compare to previous reports? In Spinner and colleagues' study[2] and in the participants in the ACTT-1 cohort who presented with moderate COVID-19 at admission,[3] remdesivir resulted in some benefit in predefined clinical outcomes compared with standard of care, particularly when treatment was started early after symptom onset. In patients with severe COVID-19, the ACTT-1 trial showed faster time to improvement with remdesivir, again especially when treatment began early after symptom onset.[3] However, enthusiasm was rapidly subdued by the results of the WHO Solidarity trial, which showed no effect of remdesivir on in-hospital mortality or time to discharge.[4] Importantly, systemic steroids were more frequently used in the Solidarity (47·6%) and DisCoVeRy (40%) trials than in the ACTT-1 trial (23%), which might explain some of the observed differences.

Although the absence of mortality benefit in Solidarity seems irrefutable, death is not the only relevant outcome. The results of DisCoVeRy are thus a valuable addition to the evidence to verify the effect of remdesivir on other clinically important endpoints. But will the negative findings of the DisCoVeRy trial finally settle the case for remdesivir, or do some of the study limitations leave some room for cautious optimism?

First, by comparing the clinical status at a fixed timepoint, the DisCoVeRy trial risked missing the optimal time to assess clinical benefit. 15 days might be too late to observe differences in patients who do not progress to mechanical ventilation and too soon in patients who do. Although time-to-event analyses aim to circumvent this problem, the commonly used time-to-improvement endpoint might also be contested in this case. The rationale behind the use of antiviral drugs is mainly to reduce the viral load and thereby mitigate disease progression rather than cause improvement. Therefore, time to deterioration might be a preferred endpoint. Indeed, Ader and colleagues[1] reported a lower hazard of mechanical ventilation, ECMO, or death in patients treated with remdesivir than in those treated with standard of care in a subgroup of patients who were not on mechanical ventilation at baseline. This finding is consistent with a post-hoc analysis of the ACTT-1 trial (HR for time to mechanical ventilation or death 0·67 [95% CI 0·52–0·87])[5] but inconsistent with a prespecified analysis in the Solidarity trial (rate ratio for initiation of mechanical ventilation or death 0·97 [95% CI 0·85–1·10]).

Second, there is inherent bias with an open-label design. The ordinal scale is prone to a degree of subjectivity, causing concern of a more optimistic interpretation of the clinical status of treated patients. On the other hand, with intravenous treatment, patients might be kept longer at the hospital to complete active treatment, as observed in both the Solidarity trial and the study by Spinner and colleagues.[2]

Last, median time from symptom onset to treatment initiation was 9 days (IQR 5–10) in the DisCoVeRy trial. This is similar to the other trials with hospitalised patients, and long after the peak in viral load will have passed in most patients. This might explain why no effect of remdesivir on viral clearance was seen in any of these studies.[6] As such, the DisCoVeRy results cannot deny or confirm a possible benefit in patients with rapidly progressive disease who present early or who are immunocompromised, the real-world clinical scenario in which remdesivir is most likely to still be considered.

In conclusion, remdesivir might have a clinically meaningful benefit in well selected patients that deserves further exploration. It will be important to compare its clinical effects with those of approved monoclonal antibodies. However, remdesivir's potential benefit in addition to steroids and other approved immunomodulators such as baricitinib and tocilizumab is highly uncertain. As findings from DisCoVeRy show an absence of effect on late clinical status and mortality, there is no reason to advocate remdesivir use outside of clinical trials.

We declare no competing interests.

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