
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

# The place for remdesivir in COVID-19 treatment


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Finding antivirals that reduce mortality from severe respiratory viral infections has proven challenging. Phase 3 trials of baloxavir and pimodivir for severe influenza were unsuccessful (NCT03684044 and NCT03376321). Lopinavir–ritonavir and hydroxychloroquine are not efficacious in treating COVID-19.[1,2] Interim results from the WHO-led, open-label, randomised SOLIDARITY trial[3] of patients with COVID-19 report that 301 (11·0%) of 2743 patients analysed who received remdesivir and 303 (11·2%) of 2708 patients analysed who received standard care died by day 28 (Kaplan-Meier rate ratio [RR] 0·95, 95% CI 0·81–1·11; p=0·50). Final results from the ACTT-1 study[4] sponsored by the National Institute of Allergy and Infectious Diseases are broadly similar: this randomised, placebo-controlled trial of patients with COVID-19 reported a 29-day mortality of 11·4% in 541 individuals assigned remdesivir and 15·2% in 521 assigned placebo (hazard ratio [HR] 0·73, 95% CI 0·52–1·03).[4]

The characteristic immunopathology of COVID-19 might explain these disappointing results. An initial phase of intense viral replication progresses to respiratory failure at day 8–9 in severe infections due to the host inflammatory response.[5] Although severe acute respiratory syndrome coronavirus 2 is still detectable during the hyperinflammatory phase, viral concentrations are substantially lower in this phase than in the first week of illness.[6] Suppressing hyperinflammation with corticosteroids was shown to be efficacious at reducing mortality in the RECOVERY trial, with the greatest benefit among those requiring mechanical ventilation (mortality 29·3% in the dexamethasone group *vs* 41·4% in the usual care group; RR 0·64, 95% CI 0·51–0·81).[7]

This natural history suggests a window of opportunity for antivirals before fulminant inflammation sets in. In the SOLIDARITY trial,[3] there was a trend towards reduced mortality with remdesivir among patients requiring low-flow or high-flow oxygen at baseline, but not among those requiring mechanical ventilation at baseline, albeit without reaching statistical significance (12·2% in the remdesivir group *vs* 13·8% in the control group; RR 0·85, 95% CI 0·66–1·09). Among the subset of patients in the ACTT-1 trial[4] requiring oxygen supplementation but not high-flow oxygen or ventilatory support, remdesivir had a significant mortality benefit (4·0% in the remdesivir group *vs* 12·7% in the control group; HR 0·30, 95% CI 0·14–0·64). Although the credibility of post-hoc subgroup analysis is questionable, the concordant results suggests this finding is not due to chance.

Rather than mortality, the primary endpoint for the ACTT-1 trial[4] was time to clinical recovery, defined as either discharge from hospital or continued hospitalisation without the need for supplemental oxygen or ongoing medical care. Median time to recovery improved from 15 days (95% CI 13–18) for those given placebo to 10 days (9–11) for those given remdesivir (RR 1·29, 95% CI 1·12–1·49). In subgroup analyses, the reduction in time to recovery was only statistically significant in patients randomly assigned 10 days or fewer from symptom onset. Similarly, in a prematurely terminated trial of remdesivir in China, patients with COVID-19 and symptom duration of 10 days or less who received remdesivir clinically improved faster than did those who received placebo (HR 1·52, 95% CI 0·95–2·43).[8] No comparable recovery rate data are available from the SOLIDARITY trial.[3]

So, what currently is the role of remdesivir in COVID-19 treatment? For patients with mild or moderately severe COVID-19 and no need for respiratory support, remdesivir does not offer significant benefit at day 28 and its use is not recommended.[9] For individuals at high risk of hyperinflammation who are diagnosed early during illness (≤10 days) and require supplemental oxygen, remdesivir shortens the time to recovery and reduces the risk of progression. This clinically important endpoint is cost-effective in some health-care settings.[10]

The risks and benefits of remdesivir in patients presenting with severe COVID-19 who require high-flow oxygen or mechanical ventilation are uncertain. Adverse event reporting from the ACTT-1[4] trial and the paper by Yeming Wang and colleagues[8] indicate that there is a low risk of remdesivir causing harm, but knowing whether it has any additive effect in combination with corticosteroids is crucial. Studies of investigational agents, such as immunomodulators and monoclonal antibodies, in critically ill patients should also examine the effects of combination therapies with remdesivir by use of a placebo-controlled design.

Further assessment of the effects of remdesivir on the inflammatory response and virological dynamics would be useful to define its role. Virological data from the ACTT-1 trial[4] are eagerly awaited as there was no difference in the decline in viral titres between remdesivir and placebo in the study by Wang and colleagues.[8]

Optimism surrounding forthcoming results from phase 3 COVID-19 vaccine trials should not deflect from the search for an effective therapeutic. Findings from the impressive SOLIDARITY trial[3] demand a re-examination of remdesivir, but in the context of other high-quality studies. For now, remdesivir is an important COVID-19 treatment option only in selected patient groups.

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*Barnaby Young, Thuan Tong Tan, Yee Sin Leo
**barnaby_young@ncid.sg**

National Centre for Infectious Diseases, Singapore 308442, Singapore (BY, YSL); Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore, Singapore (BY, YSL); Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore (BY, YSL); Department of Infectious Diseases, Singapore General Hospital, Singapore, Singapore (TTT); Duke-NUS Medical School, Singapore, Singapore (TTT); and Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore (YSL)

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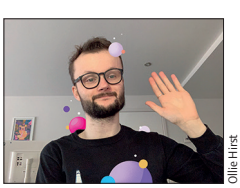
# Our cover artist for 2021

With the beginning of 2021, we take the opportunity to thank Simone Rotella, our cover artist for 2020, for his amazing creativity when almost every month the topic for the cover was the same: severe acute respiratory syndrome coronavirus 2. We wish Simone the best for his new role as cover artist for our sister journal, *The Lancet Rheumatology*, for 2021. In the meantime, we are happy to announce that Ollie Hirst, a young British artist represented by the Making Pictures company, will be creating the cover images for *The Lancet Infectious Diseases* for all 2021 and his first work can be found on the cover of this issue.

With his bold use of colours and attention to the brief, Ollie was the winner of our competition among emerging artists to become the cover artist for *The Lancet Infectious Diseases* for 2021. Born in Widnes, a city not far from Liverpool and famous for its chemical industry, Ollie now lives in Manchester where he is pursuing a career as an illustrator and graphic artist and is enjoying the city vibe (but not the canal geese). His main interests are drawing, videogames, and tennis. Current events and his own life are his main inspirations and stylistically, he loves the wit of Christoph Niemann and the fluidity of Malika Favre. Luckily for us, he particularly enjoys editorial work and in the past year his work has been markedly oriented towards representing the impact of COVID-19 in various contexts. Ollie has expressed excitement about the opportunity to work with *The Lancet Infectious Diseases* at a moment in history when an infectious disease is dominating the headlines. We are really looking forward to working with Ollie throughout 2021 on making our covers engaging and original.

*Marco De Ambrogi*


Ollie Hirst


Ollie Hirst/Making Pictures