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.

When and which patients should receive remdesivir?

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Despite 2 years having passed since the start of the COVID-19 pandemic, there is still intense debate about the best therapeutic strategy for patients with COVID-19. Multiple randomised studies have evaluated the efficacy of different antiviral,[1,2] anti-inflammatory, and antithrombotic treatments. However, results have been disparate and difficult to interpret at times due to conflicting results; some trials have reported that treatments reduce mortality and other trials, reporting on the same treatment, have shown mortality to be unaffected. Consequently, reaching a consensus on first-line treatment for hospitalised patients with COVID-19 at both local and international levels has been challenging.

Part of the uncertainty is due to the complexity of COVID-19 disease, manifesting in those severely affected as different and overlapping pathophysiological phenotypes among different people—mainly viral pneumonia, hyperinflammatory response, thrombotic events, organising pneumonia, heart failure, or co-infections (such as bacterial or fungal infections). Indeed, presentations of the range of physiological conditions listed above are clinically similar: fever, dyspnoea or respiratory failure (or both) with the need for oxygen therapy, thus requiring hospital admission. Therefore, treatment or combination treatments considered most appropriate can vary among patients.[3,4] However, most randomised studies assessing response to specific treatments have, to date, included all patients with COVID-19, irrespective of phenotype assessment.

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In *The Lancet*, the WHO Solidarity Trial Consortium report their assessment of the prognostic impact of remdesivir and three other drugs in an unmasked, open-label trial that included, across 35 countries, 14 221 adults hospitalised with COVID-19.[5] Participants were randomly allocated to receive, or not, whichever of the four study drugs (lopinavir, hydroxychloroquine, interferon-β1a, or remdesivir) was locally available at the time; no placebos were given. All patients received the local standard of care. Each drug was compared only against its own control group. The cohort was 38% women; 45% of participants were aged 50–69 years and 54% came from Asia and Africa. All analyses were done in the modified intention-to-treat population (ie, according to the assigned treatment), excluding patients with a refuted COVID-19 diagnosis or consent not encrypted into the database.

The focus of the authors' discussion in the new Article is on remdesivir treatment. By contrast to their interim study that showed no decrease in mortality for patients receiving remdesivir,[1] the new Article reports both a decrease in mortality among non-ventilated adults with oxygen therapy (remdesivir 14·6% *vs* control 16·3%; RR 0·87 [95% CI 0·76–0·99], p=0·04) and a lower progression to mechanical ventilation or death (23·7% *vs* 27·1%; RR 0·83 [0·75–0·93], p=0·001) in patients receiving remdesivir. Duration of hospital stay was not the main objective of the study and this outcome could be biased by the choices made by treating physicians or the need for intravenous treatment (or both). The results showed that remdesivir use did not improve mortality risk in ventilated patients (remdesivir 42·1% *vs* control 38·6%; RR 1·13 [0·89–1·42], p=0·32). A potential explanation is that hyperinflammation, thrombosis, or co-infection

are frequent causes of patient deterioration that result in admission to an intensive care unit and the need for mechanical ventilation—often several days after symptom onset. In this respect, perhaps other co-adjuvant treatments or co-infections, which are not discussed in depth in the Article, are more important than antiviral treatments. The authors do not rule out that patients with a high viral load requiring early admission to an intensive care unit might not benefit from the inclusion of antiviral strategies in their care.

A clear limitation of the trial is not including data on days since symptom onset to remdesivir use, viral load as measured by cycle threshold values, or viral antigen levels (or even viraemia). These factors might prove more suitably integral in evaluating the effectiveness of remdesivir.

These new findings are in line with other publications that show improved outcomes in patients with COVID-19 receiving remdesivir.[2,6] The common denominator across this research is the reporting of better outcomes during the initial disease stage, when the viral component is high. Physicians should remember that some patients, especially those who are immunocompromised, might have elevated viral loads for months after symptom onset.

Nonetheless, other studies have not shown a positive effect of remdesivir for COVID-19.[1,7] The most likely explanation for the conflicting findings might be that clinical phenotypes differ among patients. For example, in one of the negative studies, a randomised, double-blind, multicentre trial of remdesivir versus placebo in China,[7] the median time between symptom onset and remdesivir administration was 11 days (IQR 9–12), and 19% of the patients included had undetectable viral RNA on the nasopharyngeal and oropharyngeal swab taken at baseline, despite being PCR-positive at enrolment.

The COVID-19 pandemic has presented various turning points in epidemiology, which are not entirely reflected over the course of the Solidarity trial —for example, the emergence of multiple viral variants causing disease with varying severity and ability for replication,[8,9] including a SARS-CoV-2 delta variant (B.1.617.2) wave during which young patients often required admission to an intensive care unit quickly after hospitalisation.[10] Due to the inclusion periods established for Solidarity, patients with the delta or omicron (B.1.1.529) variants—which are in current circulation worldwide—were not considered for inclusion in the study.

In addition, it is unclear what effect remdesivir or any other antiviral treatment has irrespective of vaccination status. The aim of Solidarity was not to answer this question, of course. Nevertheless, most patients included in Solidarity are unvaccinated, which does not reflect the present reality of the pandemic, where vaccination rates in many countries are high. Knowing the prognostic impact of remdesivir in the current hospitalised population (eg, the older or the immunocompromised), who are likely to be vaccinated, is a needed subject of further research.

Still, the research conducted by the WHO Solidarity Trial Consortium[5] adds meaningfully to the evidence base by demonstrating that we now know remdesivir can reduce the risk of death or progression of mechanical ventilation (or both) in hospitalised patients with COVID-19 requiring oxygen therapy. A great strength of Solidarity is the inclusion of a very large number of patients from many clinical centres around the world. Conversely, the absence of concordance with the current reality—in which patients are likely to be vaccinated and variants continue to emerge—is a limitation. Debate about when and which patients should receive remdesivir or co-adjuvant treatments will, therefore, continue.

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Subacromial balloon spacer for irreparable rotator cuff tears

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Rotator cuff tears are common and painful injuries, involving the muscles and tendons surrounding the glenohumeral joint of the shoulder. These tears can be treated with surgical repair, or they sometimes respond to exercise therapy and rehabilitation.[1] In *The Lancet*, Andrew Metcalfe and colleagues[2] report on the effect of the InSpace balloon (Stryker, USA), an innovative surgical device in orthopaedics for rotator cuff tears in the shoulder. The START:REACTS trial[2] serves three important purposes: first, it provides rigorous evidence for the efficacy of a potentially new treatment for patients with a rotator cuff tear; second, it demonstrates a new adaptive design, which might prove useful for future surgical trials; third, it highlights the development of scientific evaluation in surgery and device assessment.

The blinded, adaptive randomised controlled START:REACTS trial,[2] conducted in 24 hospitals, randomly assigned 117 patients with rotator cuff tears requiring surgery—61 patients to arthroscopic subacromial debridement only and 56 patients to the same procedure, including the InSpace balloon. The mean age of participants was 67 years (SD 8·3); 50 (43%) patients were female. The primary outcome was the Oxford Shoulder Score at 12 months. The trial was stopped at the first interim analysis as the predefined stopping boundary for futility was reached. The InSpace balloon was found to be inferior to debridement only at an early stage in the evaluation process. The mean Oxford Shoulder Score at 12 months was 34·3 in the debridement only group (n=59 with primary outcome data) and 30·3 in the debridement with device group (n=55 with primary outcome data; mean adjusted difference for adaptive design −4·2 [95% CI −8·2 to −0·26]; p=0·037). Notably, there was no difference in adverse events between the two groups. The study showed that the InSpace balloon, which aimed to provide a superior healing environment and shoulder biomechanics, did not work and should not be used. The outcome was worse than non-effectiveness; the InSpace balloon might potentially be detrimental.


Dr P Marazzi/Science Photo Library

The study utilised a well considered, innovative design. The adaptive approach, which allowed early data to inform key decision making, was new.[3] This approach has implications for the cost and longevity of future surgical trials. It is commendable that the study was done on an externally valid population, who were likely to benefit from the new technology should the spacer be effective. The fair subject selection factor is an important one, with some trials testing new medical interventions in low-resource settings. Such trials, which expose participants to potential risks, might show benefits of medications or devices that are unavailable to the population studied. Although