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Remdesivir saves lives. Were 3 years needed to learn that?



In *The Lancet Respiratory Medicine*, Alain Amstutz and colleagues¹ address a 3-year-old controversy: does remdesivir reduce mortality in patients hospitalised for COVID-19?

Remdesivir is a viral RNA polymerase inhibitor that was evaluated in patients hospitalised for COVID-19 in February, 2020, in the National Institutes of Health (NIH) Adaptive COVID-19 Treatment Trial (ACTT-1)²—a federally funded, placebo-controlled, double-blind, randomised stratified trial that enrolled 1062 patients and was completed in 59 days. ACTT-1 showed a significantly shorter time to recovery with remdesivir than with placebo (5 days shorter overall, and 7 days shorter for the sickest patients), 50% faster improvement in clinical status, 30% lower progression to non-invasive ventilation, 43% lower progression to invasive mechanical ventilation, and 45% reduction in mortality at 14 days—all prespecified endpoints with significant results.² In April, 2020, the ACTT-1 data safety monitoring board recommended to stop the trial because of the significant benefits of remdesivir, and all patients receiving placebo were offered remdesivir on the basis of unanimous ethical justification.

The results of ACTT-1 were straightforward: remdesivir was associated with faster time to recovery, shorter length of hospital stay, decreased progression to mechanical ventilation, and lower mortality, all of which are patient-centered outcomes fully relevant to clinical care. At that time, the amendment of major medical guidelines in accordance with the results of ACTT-1 would have been expected in order to immediately benefit patients hospitalised for COVID-19. However, both the Infectious Diseases Society of America (IDSA)³ and NIH⁴ guidelines recommended remdesivir only for patients on supplemental oxygen. These recommendations were made even though the 95% CIs of all respiratory support subgroups overlapped and treatment heterogeneity (interaction) was absent, which indicated that the benefits of remdesivir were similar among subgroups. The WHO guidelines did not recommend treatment with remdesivir at all, and a recommendation against its use in patients hospitalised with COVID-19 was subsequently made⁵ on the basis of the interim results of the open-label Solidarity trial.⁶ The final results⁷ of the Solidarity

trial showed that treatment with remdesivir led to significant hospital mortality reduction in patients with or without supplemental oxygen (rate ratio 0.86 [95% CI 0.76–0.98]) and significantly lower progression to mechanical ventilation or death (0.84 [0.75–0.93]).

The individual patient data meta-analysis by Amstutz and colleagues¹ featured prespecified analyses according to group allocation, standardised outcome definitions, and adverse events stratified by organ systems. The study evaluated data from a total of 10 480 patients in eight randomised controlled trials and concluded that remdesivir significantly reduces mortality in patients hospitalised with COVID-19 with or without supplemental oxygen (adjusted odds ratio [aOR] 0.80 [95% CI 0.70–0.93]). A further significant reduction is also seen in the progression to mechanical ventilation or death with remdesivir (0.63 [0.48–0.83]). A conclusion could not be reached for patients receiving ventilation owing to a lack of statistical power. In terms of patient safety, the meta-analysis showed that—both overall and by organ system—grade 3 or 4 adverse events and serious adverse events were not increased with remdesivir. Notably, these results confirm the findings of ACTT-1 that were reported in April, 2020.² Additionally, it should not be surprising that if remdesivir significantly reduced mortality in patients receiving supplemental oxygen,² patients given remdesivir earlier in the course of COVID-19 should also benefit: such findings were shown by the Solidarity trial⁷ and this meta-analysis¹ (significantly better survival and lower progression to mechanical ventilation or death in hospitalised patients with or without supplemental oxygen); by multiple large, real-world, comparative effectiveness studies from different countries^{8–11} (significantly better survival and clinical recovery in hospitalised patients without supplemental oxygen); and by the PINETREE trial¹² (significantly lower progression to hospitalisation or death in outpatients at high risk without supplemental oxygen).

In summary, this individual patient data meta-analysis¹ adds relevant scientific evidence and supports both the lower progression to mechanical ventilation and the significant survival benefits of remdesivir for patients hospitalised for COVID-19 with or without supplemental oxygen. The study suggests



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individualising approaches to remdesivir treatment for patients on mechanical ventilation, a practical example being continuing remdesivir in order to combat progressive respiratory failure due to persistent SARS-CoV-2 viral replication. Prioritising underpowered subgroup results instead of powered overall results helped to prevent the NIH and IDSA guidelines from recommending remdesivir to patients hospitalised for COVID-19 without supplemental oxygen for nearly 2 years, and prioritising the interim results of a high risk of bias trial⁶ over the complete and beneficial results of a low risk of bias trial² helped to prevent the WHO guidelines from recommending remdesivir to any patients for almost 3 years. In the context of a deadly pandemic, it would have been beneficial for these panels to have erred on the side of inclusiveness and benefit rather than focusing on subgroup and interim results as evidence of no benefit, particularly in light of the robust and positive prespecified overall outcome findings of a placebo-controlled, double-blind, randomised stratified trial² with a reassuring patient safety profile (no difference in adverse events between remdesivir and placebo) and the strong biological and clinical plausibility that antiviral benefit would extend to patients in the earlier stages of COVID-19 (before requiring supplemental oxygen). Regrettably, the delays in recommendation of remdesivir for patients—even after the initial remdesivir shortage was resolved—adversely shaped antimicrobial policy in hospitals around the world, preventing patients from receiving timely remdesivir. How many more lives could have been saved had remdesivir been recommended more broadly and made more readily available? All of us—the scientific community, public health agencies, professional societies, journal editors, and guideline committees—must learn from these mistakes to provide

more reliable scientific recommendations to directly benefit the individual care of patients globally, and to advocate for equitable access to safe and life-saving antiviral therapies such as remdesivir in low-income and middle-income countries.

I was an investigator for the federally funded National Institutes of Health Adaptive COVID-19 Treatment Trials.

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Weaning from mechanical ventilation in intensive care units: a call for new international consensus guidelines

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In *The Lancet Respiratory Medicine*, Tàì Pham and colleagues¹ report the results of the WEAN SAFE study, aiming to describe the epidemiology, management, timings, risk for failure, and outcomes of weaning in patients requiring at least 2 days of invasive mechanical

ventilation. WEAN SAFE was an international, multi-centre, prospective, observational study including 5869 critically ill adult patients, conducted in 481 intensive care units in 50 countries.¹ The authors can be congratulated for this large convenience sample