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Complement C5a inhibition: a new form of COVID-19 treatment for mechanically ventilated patients?

The relentless course of COVID-19 is a constant reminder of the fact that rigorous science remains the most relevant tool to defeat this disease and to improve patient care and public health.\(^1\)

Effective and safe antiviral drugs are necessary to treat COVID-19 and prevent progression to severe disease, morbidity, and mortality. Three antiviral drugs have shown significant benefit by decreasing the progression to severe COVID-19 disease or death in placebo-controlled, double-blind, randomised trials (remdesivir in patients admitted to hospital\(^1\) and high-risk outpatient settings,\(^4\) and nirmatrelvir–ritonavir\(^5\) and molnupiravir\(^6\) in the high-risk outpatient setting). Although these antivirals effectively improved survival outcomes, a proportion of patients still progressed to more severe disease, partly because of a dysregulated immune response to SARS-CoV-2 infection. This concept was tested in several clinical trials and led to the discovery of immunomodulatory drugs for the treatment of COVID-19. Janus kinase inhibitors significantly decreased progression to mechanical ventilation or death in five placebo-controlled, double-blind, randomised trials and one open-label trial (treatment effect with and without antiviral drugs and SARS-CoV-2 vaccines),\(^7\) whereas corticosteroids and IL-6 inhibitors reduced mortality in open-label trials but not in placebo-controlled randomised trials (treatment effect without antiviral drugs and SARS-CoV-2 vaccines).\(^13,14\) Based on this cumulative evidence from randomised trials, antivirals and immunomodulatory agents have become part of the standard of care for the treatment of COVID-19.\(^15\)

Alexander Vlaar and colleagues\(^16\) performed a placebo-controlled, double-blind, randomised phase 3 trial to evaluate the complement C5a inhibitor vilobelimab plus standard of care versus placebo plus standard of care, with 28-day mortality as the primary outcome. The study enrolled 369 patients in mechanical ventilation with COVID-19 from 46 hospitals in eight countries from October, 2020, to October, 2021. Vilobelimab decreased mortality in invasive mechanically ventilated patients with COVID-19 (hazard ratio [HR] 0·73 [95% CI 0·50–1·06]; p=0·094, stratified by site; and HR 0·67 [0·48–0·96]; p=0·027, without stratification [treatment effect without antiviral drugs and vaccines]). Frequency and severity of adverse events were similar between the groups, study drug discontinuation was 2% in each group (four [2%] patients in the vilobelimab group vs three [2%] in the placebo group), and the attrition rate was 5% (nine [5%] vs nine [5%]). Sample sizes were too small to detect differences in secondary infections induced by complement inhibition, which might be due to selective blocking of C5a by vilobelimab, not affecting the C5b-dependent membrane attack complex.

The revised prespecified primary analysis using a site stratified Cox model did not produce a statistically significant result, but the original unstratified analysis did. A prespecified logistic regression with multiple imputation supported the overall study results (age-adjusted odds ratio 0·62 [95%CI 0·40–0·95]; p=0·029). Nonetheless, given that a Cox model was the primary analysis, the central question remains whether site stratified or unstratified results should be prioritised. Survival methods, such as the Cox model, compare the observed number of treatment deaths with the number expected. Each death came from a person in the risk set—the people randomly assigned and still alive just before a death—and with no covariate adjustment, each person in the risk set is considered equally likely to have been the decedent. That assumption is questionable when there are large site-to-site risk differences unexplained by covariates. Stratification accounts for such differences by restricting the risk set to patients at the same site as the decedent, improving patient comparability and lending more credence to the equally likely assumption. Notably, the site-stratified Cox model excludes sites with no events or only one patient, which in this study accounted for 61 patients from 23 sites, which could bias results in favour of a treatment effect because excluded sites with no difference in mortality support the null hypothesis. Eliminating sites with no events or only one patient increased the p value in PANAMO, which was not statistically significant with vilobelimab. Regardless of the direction of effect, having to eliminate many sites might lead to uncertainty in the
During 1 billion years of evolution, fungi have not only become masters of survival, but have actually leveraged disasters. 65 million years ago, when an asteroid strike wiped out 70% of all life on Earth by sending dusty debris into the atmosphere, fungi survived, taking advantage of the plants dying due to the lack of sunlight. Back then, fungi infected and killed reptiles in their masses, potentially contributing to the extinction of the dinosaurs.\(^1\) By contrast, fungi were not able to survive at the high body temperatures of mammals and thereby contributed to the succession of mammals as the new dominant species on Earth. Ever since the slow enrolment rate, large mortality variability across sites, small sample size, and absence of antiviral drugs and vaccines limit the generalisability of PANAMO, the study shows promising benefits of vilobelimab for mechanically ventilated patients with severe COVID-19, and provides a direction for further investigation of new treatments that target the complement system.

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1. Kalil AC. Treating COVID-19 off-label drug use, compassionate use, and randomized clinical trials during pandemics. JAMA 2020; 323: 1897–98.
2. Singer M, Kalil A. Do not just sit there, do something but do no harm: the worrying aspects of COVID-19 experimental interventions. Intensive Care Med 2021; 47: 896–98.
3. Beigel JH, Tomashek KM, Dodds LE, et al. Remdesivir for the treatment of COVID-19—final report. N Engl J Med 2020; 383: 1813–26.
4. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. N Engl J Med 2022; 386: 305–15.
5. Hammond J, Leister-Tebbey H, Gardner A, et al. Oral nimotuzib for high-risk, nonhospitalized adults with COVID-19. N Engl J Med 2022; 386: 3197–408.
6. Jayk Bernal A, Gomes da Silva MM, Musungaije DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med 2022; 386: 509–20.
7. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. N Engl J Med 2021; 384: 795–807.
8. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021; 9: 1407–18.
9. Ely EW, Ramanan AV, Kortman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med 2022; 10: 327–36.
10. Wolfe CR, Tomashok KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double-placebo-controlled trial. Lancet Respir Med 2022; 10: 888–99.
11. Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalised with COVID-19 pneumonia. N Engl J Med 2021; 385: 406–15.
12. Group RC. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. Lancet 2022; 400: 359–68.
13. Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis JAMA 2020; 324: 1330–41.
14. Shankar-Hari M, Vale CL, Godolphin PJ, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalised for COVID-19: a meta-analysis. JAMA 2021; 325: 499–518.
15. Kalil AC, Stibbling J. Baricitinib: the first immunomodulatory treatment to reduce COVID-19 mortality in a placebo-controlled trial. Lancet Respir Med 2021; 9: 1349–51.
16. Vlaar APJ, Witzenrath M, van Paassen P, et al. Anti-C-Ca antibody (vilobelimab) therapy for critically ill, mechanically ventilated patients with COVID-19 (PANAMO): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med 2022; published online Sept 7 https://doi.org/10.1016/S2213-2600(22)00297-1.