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.

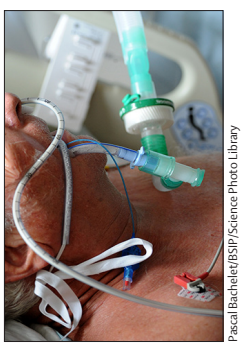
Complement C5a inhibition: a new form of COVID-19 treatment for mechanically ventilated patients?

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.[1,2]

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[3] 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),[7–12] 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



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stratified analysis in PANAMO. Whenever the p value is close to 0·05, results will not be robust to all sensitivity analyses, especially in survival analysis when the number of deaths (not the sample size) is crucial. For example, the sites in Russia included a small sample size but had a large number of deaths, thus excluding Russia from the analysis could substantially affect results. A post-hoc Cox model stratified by country (to avoid excluding sites without events) showed a HR of 0·61 (95% CI 0·43–0·87; p=0·0067), and the model stratified by the WHO COVID-19 ordinal scale (HR 0·67 [0·47–0·95]; p=0·024) and frailty (age-adjusted HR 0·65 [0·45–0·93]; p=0·018) showed similar results, which persisted at 60-day mortality.

Although 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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