Vilobelimab

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Vilobelimab is an anti-C5a monoclonal antibody. High concentrations of C5a have been reported in patients with severe COVID-19.[1] C5a activates innate immune system responses, including inflammation and the release of histamines, and can increase damage to local tissues.[2] A study in mice demonstrated that an anti-C5a monoclonal antibody reduced immune system activation and inhibited lung injury.[3] Vilobelimab targets C5a, which is a product of complement activation, and preserves membrane attack complex function.[4] Vilobelimab is not approved by the Food and Drug Administration (FDA) for any indication.

On April 4, 2023, the FDA issued an Emergency Use Authorization for the use of vilobelimab for the treatment of COVID-19 in hospitalized adults when it is administered within 48 hours of mechanical ventilation or extracorporeal membrane oxygenation.[5]

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vilobelimab for the treatment of COVID-19.

Rationale

Results from the PANAMO trial were used to support the FDA Emergency Use Authorization.[5] However, the prespecified analysis that stratified by study site showed that 28-day mortality among patients with COVID-19 who received vilobelimab was not significantly different from 28-day mortality among those who received placebo. The initially proposed primary study analysis did not stratify by study site. In the second phase of the study, the primary analysis was changed to stratify by site based on a recommendation from the FDA. The analysis that did not stratify by site demonstrated that all-cause mortality through Day 28 was significantly lower in the vilobelimab arm than in the placebo arm. Concomitant use of corticosteroids (97%) and antithrombotic agents (98%) was high in this study population. Prior or concomitant use of additional immunomodulators, such as tocilizumab (17% in the vilobelimab arm, 16% in the placebo arm) and baricitinib (3% in each arm), was low. The Panel determined that the results from the PANAMO trial were insufficient to recommend either for or against the use of vilobelimab for the treatment of COVID-19.

Monitoring, Adverse Effects, and Drug-Drug Interactions

Reports of adverse effects of vilobelimab are limited to a Phase 3 trial that included critically ill adult patients with COVID-19 who received intravenous vilobelimab 800 mg for up to 6 doses.[5,6] Common adverse reactions (i.e., those with an incidence ≥3% and that were observed at least 1% more frequently in the vilobelimab arm than in the placebo arm through Day 60) were pneumonia, sepsis, delirium, pulmonary embolism, hypertension, pneumothorax, deep vein thrombosis, herpes simplex, enterococcal infection, bronchopulmonary aspergillosis, increased hepatic enzymes, urinary tract infection, hypoxemia, thrombocytopenia, pneumomediastinum, respiratory tract infection, supraventricular tachycardia, constipation, and rash.

Vilobelimab is not expected to be associated with any pharmacokinetic drug-drug interactions.

Considerations in Pregnant People

There are no data on the use of vilobelimab during pregnancy, as pregnant individuals were excluded from the PANAMO trial.

Considerations in Children

There are no data on the use of vilobelimab in children. Vilobelimab is not authorized by the FDA for the treatment of COVID-19 in pediatric patients.

Clinical Data

The small (n = 30) Phase 2 portion of the Phase 2/3 PANAMO trial was too underpowered to draw any conclusions about study outcomes, including physiologic improvement at 5 days and mortality.[7]

The Phase 3 portion of the trial was a double-blind, randomized trial performed at 46 hospitals in Western Europe (i.e., Netherlands, France, Germany, Belgium), Brazil, Mexico, Russia, Peru, and South Africa from October 1, 2020, to October 4, 2021.[6] The trial compared the use of vilobelimab plus standard of care with placebo plus standard of care in patients aged ≥18 years who had laboratory-confirmed SARS-CoV-2 infection, were receiving mechanical ventilation (and were within 48 hours of intubation), and had a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of 60 to 200 mm Hg at study entry. Vilobelimab 800 mg was administered intravenously on Days 1, 2, 4, 8, 15, and 22, if the patient remained hospitalized, for a maximum of 6 doses.

The primary outcome was all-cause mortality at 28 days. Secondary outcomes included all-cause mortality at 60 days, the proportion of patients who improved on a World Health Organization 8-point ordinal scale, the proportion of patients who developed acute kidney failure by Day 28, and the proportion of patients free from renal replacement therapy at Day 28.

Results

- The trial enrolled 369 patients; 368 patients were included in the analysis that did not stratify by study site (177 in the vilobelimab arm, 191 in the placebo arm).
- In the prespecified analysis that stratified by study site (n = 307), 28-day mortality was not significantly different between the vilobelimab and placebo arms (HR 0.73; 95% CI, 0.50–1.06; $P = 0.094$). The analysis for 28-day mortality that stratified by study site excluded the 61 patients (16.6%) from sites that had no deaths or had only 1 treatment group.
- In the analysis that did not stratify by study site (n = 368), 28-day mortality was lower in the vilobelimab arm than in the placebo arm (54 of 177 patients [31%] vs. 77 of 191 patients [44%]), and the difference between arms was statistically significant (HR 0.67; 95% CI, 0.48–0.96; $P = 0.027$).
- Prespecified subgroup analyses identified a significant reduction in 28-day mortality in the vilobelimab arm for subgroups of patients with severe acute respiratory distress syndrome (HR 0.55; 95% CI, 0.30–0.98; $P = 0.044$), patients with an estimated glomerular filtration rate of <60 mL/min (HR 0.55; 95% CI, 0.31–0.96; $P = 0.036$), and patients receiving mechanical ventilation and additional organ support (category 7 on the World Health Organization 8-point ordinal scale; HR 0.62; 95% CI, 0.40–0.95; $P = 0.028$).
- In a prespecified analysis of the Western Europe subgroup (i.e., Netherlands, France, Germany, Belgium), the vilobelimab arm had significantly lower 28-day mortality than the placebo arm (HR 0.51; 95% CI, 0.30–0.87; $P = 0.014$).

- For the secondary outcomes:
  - The analysis that stratified by study site showed no significant difference between the arms for all-cause mortality at 60 days (HR 0.74; 95% CI, 0.52–1.04; $P = 0.082$).
  - The vilobelimab arm had significantly fewer patients who required renal replacement therapy at Day 28 than the placebo arm (age-adjusted HR 0.54; 95% CI, 0.30–0.98; $P = 0.042$).

Limitations

- The results for the study's site-stratified, prespecified analysis were not significant.
- The analysis for 28-day mortality that stratified by study site excluded the 61 patients (16.6%) from sites that had no deaths or had only 1 treatment group.
- Very few patients received a second immunomodulator (tocilizumab or baricitinib), which makes the study results difficult to apply to current practice.
- Compared to other studies that have evaluated the use of immunomodulators for the treatment of COVID-19, Phase 3 of the PANAMO trial had a relatively small sample size.

References

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