

# Interleukin-1 Inhibitors

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Endogenous interleukin (IL)-1 is elevated in patients with COVID-19.<sup>1-3</sup> In addition, SARS-CoV-2 infection causes epithelial damage that leads to the release of IL-1 beta, which recruits inflammatory cells and induces the release of IL-1 beta in monocytes. This in turn leads to the release of more IL-1 to recruit and activate additional innate immune cells. Drugs that block the IL-1 receptor (e.g., anakinra) or drugs that block IL-1 signaling (e.g., canakinumab) can potentially interrupt this autoinflammatory loop. These drugs have been investigated as potential treatments for COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved by the Food and Drug Administration (FDA) to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.<sup>4</sup> It is used off-label to treat severe chimeric antigen receptor T cell-mediated cytokine release syndrome and macrophage activation syndrome/secondary hemophagocytic lymphohistiocytosis. On November 8, 2022, the FDA issued an Emergency Use Authorization for anakinra. The Emergency Use Authorization allows the use of anakinra to treat COVID-19 in certain hospitalized adults with pneumonia. These patients must have laboratory-confirmed SARS-CoV-2 infection, require supplemental oxygen (either low- or high-flow oxygen), be at risk of progressing to severe respiratory failure, and be likely to have elevated plasma levels of soluble urokinase plasminogen activator receptor (suPAR), a marker of inflammation.<sup>5</sup>

Canakinumab is a human monoclonal antibody that targets the beta subunit of IL-1 and is approved by the FDA for the treatment of systemic juvenile idiopathic arthritis, Still's disease, and gout.<sup>6</sup>

## Recommendations

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of anakinra for the treatment of COVID-19.
- The Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial (BIIa).

## Rationale

In the SAVE-MORE trial, 594 hospitalized patients who had moderate or severe COVID-19 pneumonia and plasma suPAR levels  $\geq 6$  ng/mL were randomized to receive either anakinra or placebo.<sup>7</sup> The study found that patients who received anakinra had a lower risk of clinical progression of COVID-19 than those who received placebo. REMAP-CAP, an open-label, adaptive platform trial that evaluated the use of several immunomodulators in patients with COVID-19 who required organ support, found no clinical benefit of anakinra in these patients. In addition, among patients who received anakinra, no reduction in mortality was observed during a 180-day follow up.<sup>8</sup> Several smaller trials that evaluated the use of anakinra in people with COVID-19 were either stopped early due to futility or did not detect a benefit of anakinra in these patients.<sup>9-11</sup> Meta-analyses of the available data have not detected a benefit of using anakinra to treat COVID-19.<sup>12,13</sup>

The SAVE-MORE study population was restricted to participants with high levels of suPAR ( $\geq 6$  ng/mL) based on the hypothesis that this group is most likely to benefit from IL-1 inhibition. However, the laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States. Using data from the SAVE-MORE and SAVE trials (both a priori, open-label, single-arm prospective studies), the FDA developed a scoring system that uses common

clinical and laboratory factors to identify patients who are likely to have suPAR levels  $\geq 6$  ng/mL.

The Panel has concluded that there is insufficient evidence to recommend either for or against the use of anakinra for the treatment of COVID-19. After reviewing the available evidence, the Panel notes the following:

- Data from randomized trials have not consistently demonstrated a benefit of using anakinra to treat COVID-19.
- The suPAR assays that were used to identify patients for participation in the SAVE-MORE trial are not available in the United States.
- The scoring system that the FDA developed to identify patients who are likely to have high suPAR levels requires further validation.

The Panel **recommends against** the use of **canakinumab** for the treatment of COVID-19, except in a clinical trial (**BIIa**). CAN-COVID, a randomized controlled trial that evaluated the use of canakinumab in hospitalized patients with COVID-19 who were hypoxemic but did not require ventilatory support, reported that the use of canakinumab did not improve the likelihood of survival without mechanical ventilation.<sup>14</sup> CanCovDia was a randomized controlled trial that compared the use of canakinumab to placebo in hospitalized patients with COVID-19, type 2 diabetes, and a body mass index  $>25$ . This trial did not find a difference between the arms in the occurrence of a composite outcome that included length of survival, ventilation, intensive care unit (ICU) stay, and hospitalization through Day 29.<sup>15</sup>

## Monitoring and Adverse Effects

Headache, nausea, vomiting, and liver enzyme elevations can occur with both anakinra and canakinumab.

Anakinra was not associated with any significant safety concerns when used in clinical trials for the treatment of sepsis.<sup>16-18</sup> Increased rates of infection were reported with prolonged anakinra use in combination with tumor necrosis factor- $\alpha$  blockade but not with short-term use.<sup>19</sup>

## Considerations in Pregnant People

The data on using IL-1 inhibitors to treat COVID-19 in pregnant patients are currently limited. The American College of Rheumatology recommends against the use of anakinra during pregnancy.<sup>20</sup> Unintentional first-trimester exposure to anakinra is unlikely to be harmful, given the minimal transfer of monoclonal antibodies across the placenta early in pregnancy.<sup>21</sup>

## Considerations in Children

Anakinra has been used to treat severely ill children with rheumatologic conditions, including systemic juvenile idiopathic arthritis and macrophage activation syndrome. The data on the use of anakinra in pediatric patients with acute respiratory distress syndrome or sepsis are limited. Information on the use of anakinra in pediatric patients with acute COVID-19 is limited to small case series.<sup>22,23</sup> However, anakinra has been used in approximately 10% of cases of multisystem inflammatory syndrome in children (MIS-C).<sup>24-29</sup> Anakinra is often included in institutional protocols for the treatment of MIS-C in the United States, and it is an option for second-line therapy for refractory MIS-C in national consensus guidelines, including the COVID-19 Treatment Guidelines.<sup>30-32</sup> For more information, see [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#).

Data on using canakinumab in pediatric patients are limited to use in patients with periodic fever syndromes and systemic juvenile idiopathic arthritis. There are no data on its use in pediatric patients

with acute COVID-19 or MIS-C.

## Clinical Data

### ***SAVE-MORE***

SAVE-MORE was a randomized controlled trial in 594 hospitalized patients with moderate to severe COVID-19 pneumonia and plasma suPAR levels  $\geq 6$  ng/mL.<sup>7</sup> Patients who required noninvasive ventilation (NIV) or mechanical ventilation were excluded from the study. Patients were randomized 2:1 to receive anakinra 100 mg subcutaneously once daily for 10 days or placebo. The primary endpoint was clinical status at Day 28 on the 11-point World Health Organization Clinical Progression Scale (WHO-CPS). Additional analyses assessed outcomes at Days 60 and 90.<sup>33</sup>

### **Results**

- Patients who were randomized to receive anakinra had lower odds of a worse WHO-CPS score at Day 28 (OR 0.36; 95% CI, 0.26–0.50;  $P < 0.0001$ ).
- The secondary endpoints also favored anakinra, including the absolute decrease in WHO-CPS scores from baseline at Days 14 and 28, the absolute decrease in sequential organ failure assessment (SOFA) scores from baseline at Day 7, the median time to hospital discharge, and the median duration of ICU stays.
- A smaller proportion of patients in the anakinra arm experienced secondary infections, including ventilator-associated pneumonias, than in the placebo arm (8.4% vs. 15.9%;  $P = 0.01$ ).
- Twenty-eight-day mortality was lower among patients who received anakinra than among those who received placebo (3.2% vs. 6.9%; HR 0.45; 95% CI, 0.21–0.98;  $P = 0.045$ ).
- Additional analyses performed at Days 60 and 90 showed a sustained survival benefit for anakinra.

### **Limitations**

The laboratory assay that is used to assess suPAR levels is not currently available in many countries, including the United States. The FDA worked with the SAVE-MORE investigators to develop a scoring system that predicts whether a patient has suPAR levels  $\geq 6$  ng/mL using baseline data from patients who were randomized during the trial and a subset of patients who were screened but not randomized. The FDA's surrogate for suPAR levels  $\geq 6$  ng/mL is called SCORE 2, and it includes the following patient characteristics:

- Aged  $\geq 75$  years
- Severe pneumonia, as determined by WHO criteria
- Current or past smoker
- SOFA score  $\geq 3$
- Neutrophil to lymphocyte ratio  $\geq 7$
- Hemoglobin  $\leq 10.5$  g/dL
- Medical history of ischemic stroke
- Blood urea  $\geq 50$  mg/dL and/or medical history of renal disease

Patients who met  $\geq 3$  of these criteria were considered positive for SCORE 2 and likely to have a suPAR level  $\geq 6$  ng/mL. SCORE 2 had a positive predictive value of 0.95, a sensitivity of 0.41, and specificity of 0.96 when retrospectively applied to the SAVE-MORE trial, and it had similar characteristics when applied to the SAVE trial, an open-label, single-arm prospective study that served as an external

validation dataset. In the SAVE-MORE trial, a greater proportion of patients who were positive for SCORE 2 developed severe respiratory failure at Day 14 compared with those who met  $\leq 2$  of the SCORE 2 criteria (41.4% vs. 8.0%).<sup>4,34</sup>

## **REMAP-CAP**

The REMAP-CAP trial is an open-label, adaptive platform trial in which eligible participants are randomized to several domains, including the Immune Modulation Therapy domain, which consists of 2 IL-6 inhibitors, anakinra, interferon beta-1a, and a control group.<sup>8</sup> Participants are eligible for enrollment if they are within 24 hours of receiving respiratory or cardiovascular organ support in the ICU and they have suspected or microbiologically confirmed COVID-19. This population had more advanced disease than the population enrolled in the SAVE-MORE trial.

Anakinra 300 mg was given intravenously (IV) as a loading dose, followed by anakinra 100 mg IV every 6 hours for 14 days until patients were either free from mechanical ventilation for >24 hours or discharged from the ICU. The primary outcome was measured using an ordinal scale that included a composite of in-hospital mortality and duration of respiratory and cardiovascular organ support at 21 days; all deaths up to 90 days were assigned the worst outcome. The trial used a Bayesian design that allowed the authors to compare nonconcurrently randomized interventions across time periods. Additional analyses assessed outcomes at 180 days.<sup>3,8</sup>

## **Results**

- Of the 2,274 participants who were randomized to 1 of the arms in the Immune Modulation Therapy domain, 365 individuals were assigned to receive anakinra and included in the analysis, 406 were assigned to the usual care (control) arm, 943 were assigned to receive tocilizumab, and 483 were assigned to receive sarilumab.
- Of those assigned to receive anakinra, 37% were receiving mechanical ventilation at study entry compared with 32% of patients in the other arms. The other patients received oxygen through a high-flow nasal cannula or NIV, with a few exceptions.
- The median number of organ support-free days was similar for patients who received anakinra and those who received usual care (0 days [IQR -1 to 15 days] vs. 0 days [IQR -1 to 15 days]). The aOR for organ support-free days was 0.99 for anakinra (95% CrI, 0.74–1.35), with a 47% posterior probability of superiority to control. Sixty percent of those who were assigned to receive anakinra survived compared with 63% of those who were assigned to the control arm, with a 44% posterior probability that anakinra was superior to usual care.
- Additional analyses performed at 180 days showed no reduction in mortality among patients who received anakinra.<sup>3,8</sup>
- The risk of experiencing serious adverse events was similar between the arms.

## **Limitations**

Patients were not randomized contemporaneously to receive anakinra or usual care; the treatment effect was estimated from an overarching model that mostly included patients who were randomized to receive an IL-6 inhibitor (tocilizumab or sarilumab) or usual care, and patients who were randomized to receive an IL-6 inhibitor or anakinra. Thus, the estimate of the treatment effect is not fully protected by randomization. This study also had an open-label design.

## **CORIMUNO-ANA-1**

The CORIMUNO-ANA-1 trial randomized 116 hospitalized patients with COVID-19 pneumonia 1:1 to receive either usual care plus anakinra (200 mg IV twice daily on Days 1–3, 100 mg IV twice on Day

4, and 100 mg IV once on Day 5) or usual care alone.<sup>9</sup> Patients were eligible for enrollment if they had laboratory-confirmed SARS-CoV-2 infection with COVID-19 pneumonia and they required >3 L/min of supplemental oxygen. Patients who required high-flow oxygen, ventilation, or ICU admission were excluded. The 2 coprimary outcomes were the proportion of patients who had died or who needed NIV or mechanical ventilation by Day 4 (score of >5 on the WHO-CPS) and the proportion who survived without the need for NIV or mechanical ventilation (including high-flow oxygen) by Day 14.

## Results

- There was no difference between the arms in the occurrence of the coprimary outcomes: by Day 4, 36% of patients in the anakinra arm had died or required high-flow oxygen or ventilation compared with 38% in the usual care arm (90% CrI, -17.1 to 12.0; posterior probability of benefit 61%). By Day 14, 47% of patients in the anakinra arm had died or required NIV or mechanical ventilation compared with 51% in the usual care arm (median HR 0.97; 90% CrI, 0.62–1.52; posterior probability of benefit 55%).
- Fifty-two percent of patients received corticosteroids at study entry.
- Serious adverse events occurred in 46% of patients in the anakinra arm compared with 38% in the usual care arm; 11 of 59 patients (18.6%) in the anakinra arm experienced bacterial or fungal infections compared with 4 of 55 patients (7.3%) who received usual care.

## Limitations

The limitations of this study include the small sample size, narrow eligibility criteria, and the fact that many patients did not receive current standard of care therapy (e.g., corticosteroids, remdesivir).

## *COV-AID*

The COV-AID trial enrolled 342 hospitalized patients with COVID-19, hypoxia, and signs of hyperinflammation.<sup>10</sup> This trial had an open-label, 2 x 2 factorial design to compare IL-1 inhibition to no IL-1 inhibition and IL-6 inhibition to no IL-6 inhibition. The primary outcome was the time to clinical improvement, which was defined as an increase of 2 or more points on a 6-point ordinal scale or discharge from the hospital.

## Results

- There was no difference between the anakinra arm and the usual care arm in the occurrence of the primary outcome. The estimated median time to clinical improvement was 12 days (95% CI, 10–16 days) in the anakinra arm and 12 days (95% CI, 10–15 days) in the usual care arm (HR 0.94; 95% CI, 0.73–1.21).
- Fifty-five patients died during the study, and no statistically significant differences in mortality were found between the study arms.
- The risk of experiencing serious adverse events was similar between the arms.

## Limitations

The limitations of this study include the open-label design and the fact that many patients did not receive current standard of care therapy (e.g., corticosteroids, remdesivir). In addition, the 2 x 2 factorial structure was underpowered to detect interactions between treatment arms, because some patients received both an IL-1 inhibitor and an IL-6 inhibitor.

## *ANA-COVID-GEAS*

ANA-COVID-GEAS was a multicenter, randomized, open-label, Phase 2/3 clinical trial of 179 hospitalized patients with severe COVID-19 pneumonia and hyperinflammation.<sup>11</sup> Patients were



randomized 1:1 to receive anakinra 100 mg IV 4 times daily plus standard of care or standard of care alone for up to 15 days. The length of treatment was based on the patient's clinical response per the protocol-defined criteria. The primary outcome was the proportion of patients who did not require mechanical ventilation up to 15 days after treatment initiation.

## Results

- There was no statistical difference between the anakinra arm and standard of care arm in the proportion of patients who did not require mechanical ventilation up to 15 days after treatment initiation (77.1% vs. 85.9%; relative risk ratio 0.90; 95% CI, 0.77–1.04).
- The secondary outcomes were also not statistically different between groups. These included the time to mechanical ventilation (HR 1.72; 95% CI, 0.82–3.62) and the number of deaths by Day 28 (4 vs. 5; relative risk ratio 0.77; 95% CI, 0.21–2.77).

## Limitations

Key limitations of this study were its open-label design, modest sample size, the fact that only half of the patients received dexamethasone, and the fact that the proportion of patients who required oxygen supplementation at baseline was significantly higher in the anakinra arm.

## **CAN-COVID**

CAN-COVID was a double-blind, placebo-controlled randomized trial of 454 hospitalized patients with COVID-19 who were hypoxemic but not mechanically ventilated and had elevated levels of C-reactive protein ( $\geq 20$  mg/L) or ferritin ( $\geq 600$   $\mu$ g/L).<sup>14</sup> Patients were randomized 1:1 to receive a single dose of IV canakinumab (450 mg for a body weight of 40 kg to <60 kg, 600 mg for 60–80 kg, and 750 mg for >80 kg) or placebo. The primary outcome was survival without the need for mechanical ventilation from Days 3 through Day 29.

## Results

- There was no statistical difference between the canakinumab arm and placebo arm in the proportion of patients who survived without mechanical ventilation (88.8% vs. 85.7%;  $P = 0.29$ ).
- The number of COVID-19–related deaths at 4 weeks was similar for the 2 arms (11 of 223 patients [4.9%] in the canakinumab arm vs. 16 of 222 patients [7.2%] in the placebo arm; OR 0.67; 95% CI, 0.30–1.50).
- Forty-one percent of patients in the canakinumab arm and 32% in the placebo arm received dexamethasone.
- Serious adverse events occurred in 16% of patients who received canakinumab and in 21% of patients who received placebo.

## Limitations

The use of corticosteroids was unbalanced in this study, with more patients receiving dexamethasone at baseline in the canakinumab arm than in the placebo arm. More patients received dexamethasone after the trial was underway in the placebo arm than in the canakinumab arm (22.5% vs. 14.5%), and more patients received tocilizumab in the placebo arm than in the canakinumab arm (8.8% vs. 2.2%).

## **CanCovDia**

CanCovDia was a double-blind, placebo-controlled, randomized trial of 116 hospitalized patients with type 2 diabetes, a body mass index  $>25$ , and COVID-19.<sup>15</sup> Most patients (65.8%) required oxygen supplementation. Patients were randomized 1:1 to receive a single dose of canakinumab (using weight-adapted dosing between 450 and 750 mg) or placebo. The primary outcome was reported as a win

ratio, which was calculated by dividing the number of winners by the number of losers in a sequence of hierarchical comparisons based on ordered components. This hierarchy included:

1. Longer survival time
2. Longer ventilation-free time
3. Longer ICU-free time
4. Shorter hospitalization time within 29 days after treatment with canakinumab compared with placebo

## Results

- The win ratio for canakinumab versus placebo was 1.08 (95% CI, 0.69–1.69;  $P = 0.75$ ).
- At 4 weeks, there was no statistically significant difference between the canakinumab arm and placebo arm in the number of deaths (4 vs. 7; OR 0.54; 95% CI, 0.13–1.90).

## Limitations

At baseline, patients in the canakinumab arm had poorer kidney function and higher levels of ferritin and suPAR compared to those in the placebo arm.

Other small cohort studies, case-control studies, and case series have reported mixed findings with regard to improvement in outcomes among patients who received anakinra for the treatment of COVID-19.<sup>35-38</sup> The clinical implication of these findings is uncertain due to small sample sizes and unmeasured confounding factors. Therefore, these studies did not substantially influence the Panel's current recommendations for using IL-1 inhibitors.

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