Anakinra (KINERET) for COVID-19
Frequently Asked Questions (FAQ)
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

Background

The COVID-19 pandemic caused by a novel coronavirus has resulted in significant morbidity and mortality, and therapies are needed to treat severe infections due to this virus. Anakinra (ANA) is a recombinant, nonglycosylated form of human interleukin-1 receptor antagonist (IL-1Ra), approved for use in several immunologic conditions, including rheumatoid arthritis, and on November 8th 2022, based on the results of the SAVE-MORE clinical trial, it was granted an FDA Emergency Use Authorization (EUA), making it available for treatment of hospitalized patients with severe COVID-19 who are requiring supplemental oxygen. The EUA is based on the totality of evidence, which suggests it is reasonable to believe the known and potential benefits outweigh the known and potential risks when used as described in the EUA. This FAQ is designed to serve as a resource for VHA physicians, pharmacists, nurses, and other healthcare personnel on the use of Anakinra in the management of severe COVID-19.

Anakinra: Mechanism of Action in COVID-19 and Pharmacokinetics

What is ANA and how does it work as a treatment for COVID-19?

- Anakinra is a recombinant IL-1Ra, similar to human IL-1Ra, and produced using recombinant DNA technology using an *E.coli* bacterial expression system. IL-1 is produced in response to inflammatory stimuli and by blocking the biologic activity of IL-1 alpha and beta, it modulates immune and inflammatory reactions.
- Early in the COVID-19 pandemic, it was recognized that some cases of severe COVID-19 presented with a clinical syndrome similar to CRS, or cytokine storm, including respiratory failure with elevated levels inflammatory markers. Soluble urokinase receptor (suPAR) levels have been associated with a predictive value for poor outcomes in COVID-19, and was used in the clinical trials of anakinra to identify a population likely to have poorer outcomes. Of note, suPAR levels are not commercially available in the U.S.
- At this time, the FDA EUA of ANA in COVID-19 is based on 1 randomized controlled trial, the SAVE-MORE trial
    - **NOTE: *Anakinra is NOT an FDA approved drug for the treatment of COVID-19 but is authorized for Emergency Use with a scope that is limited to patients meeting ALL criteria outlined in the EUA*.**
    - **ANA is authorized for the treatment of COVID-19 in hospitalized patients with a positive SARS-CoV-2 direct viral test who require supplemental oxygen (low or high-flow oxygen), are at risk for progressing to severe respiratory failure and are likely to have elevated plasma soluble urokinase plasminogen activator receptor (suPAR). See below under efficacy for information on patients expected to have elevated suPAR.**

What are the known Pharmacokinetic (PK) parameters of ANA?

- In rheumatoid arthritis (RA), maximum plasma concentrations after a SQ injection occur at 3-7 hours post-dose, with a terminal half-life of 4-6 hours.
    - Estimated ANA clearance increased with increasing creatinine clearance (CrCl) and body weight.
    - **PK with renal impairment:** ANA clearance in subjects with mild (CrCl 50-80 mL/min) and moderate (CrCl 30-49 mL/min) was reduced by 16% and 50% respectively. In severe renal insufficiency (CrCl < 30 mL/min) and end stage renal disease, mean plasma ANA clearance decreased by 70% and 75% respectively, and less than 2.5% of an administered dose is removed by hemodialysis or continuous peritoneal dialysis.
    - **PK with hepatic dysfunction:** No formal studies have been conducted.
- No drug-drug interaction studies are available, but studies in rats do not suggest alterations in clearance or toxicologic profile of either methotrexate or ANA when administered together. A higher rate of severe infections has been observed in patients treated with concurrent ANA and etanercept than with etanercept alone. **Use with TNF blocking agents is not recommended in the EUA.**

Anakinra Dosing in COVID-19

- **The recommended dosage of ANA for COVID-19 in adults is 100mg SQ daily for up to 10 days**
- **Preparation and Administration**
    - ANA is supplied as prefilled syringe containing 100 mg/0.67 mL ANA.

- Each pre-filled syringe is intended for single use. A new syringe should be used for each dose and any unused remaining portion discarded after dosing.
- The syringe should not be used if the solution is discolored, cloudy or if particulate matter is present.

➢ **Dose adjustments in special populations**
- **Renal insufficiency:** Consider administration of ANA 100mg every other day in patients who have severe renal insufficiency or end-stage renal disease for a total of 5 doses over 10 days.
- **Hepatic impairment:** No formal data are available on the PK of ANA in patients with hepatic impairment

Anakinra Efficacy for COVID-19 Infections

What efficacy data currently exist for the use of ANA as treatment of COVID-19 infections?

➢ **Clinical efficacy data:** The EUA approval of ANA was based on analysis of a 1 randomized-controlled trials (RCT), the SAVE-MORE trial (NCT04680949), which evaluated safety and efficacy of ANA in adults with COVID-19 pneumonia who were at risk of developing severe respiratory failure (SRF). **SAVE-MORE** was initiated after the success of the SAVE trial, a retrospective, propensity matched cohort study of hospitalized patients with COVID-19 but no evidence of respiratory failure, who had suPAR concentrations ≥ 6 ng/mL.

➢ In SAVE, at the interim analysis of 130 patients in each group, the incidence of severe respiratory failure was decreased from 59% with standard of care (SOC) to 22% with ANA (HR 0.3, 95% CI 0.2-0.46). 30-day mortality was 22% vs. 12% (p= 0.041), and ICU duration and hospital costs were also reduced with ANA treatment. No safety concerns were identified in this trial. This led to the confirmatory SAVE-MORE RCT.

➢ **SAVE-MORE:**
- **Study design**: Phase III, double-blind, RCT of ANA vs. placebo 100mg daily for 10 days in addition to standard of care (SOC) treatments

- **Inclusion**: adults:
  - Hospitalized with laboratory confirmed COVID-19
  - With radiographically confirmed pneumonia.
  - With plasma suPAR levels ≥ 6 ng/mL
- **Exclusion:**
  - pO2/FiO2 < 150 mmHg
  - Requirement for non-invasive (NIV) or invasive mechanical ventilation (MV) or ECMO
  - ANC < 1500 / mm^3 or known immunodeficiency
  - Oral or intravenous corticosteroids ≥ 0.4 mg/kg prednisone for > 15 days
  - Severe liver failure (Child-Pugh C) or end-stage renal disease
  - Pregnancy or lactation

- **Demographics:**
  - Included 405 patients who received ANA and 189 with placebo
  - Mean age was 62 years in both arms
  - Male sex 58% ANA vs. 57% placebo
  - Severe COVID-19 at start of drug 90% ANA vs. 94% placebo
    - Moderate pneumonia, 10% ANA vs. 6% placebo
  - Duration of symptoms at study drug start, median: 9 days for each group
  - Labs, (ANA vs. placebo): suPAR (7.6 vs. 7.5 ng/mL), CRP (50 vs. 51 mg/L), IL-6 (15.5 vs. 20.1 pg/mL), Ferritin (559 vs. 629 ng/mL)
  - Comorbidities (ANA vs. placebo): DM (16.3% vs. 14.8%), CKD (2.2% vs. 0.5%), CHF (3.2% vs. 2.6%)
  - Other treatments (ANA vs. placebo)
    - Oxygen (90.4% vs. 94.2%)
    - Remdesivir (73.6% vs. 74.6%)
    - Dexamethasone (84.4% vs. 88.9%)

- LMWH (95.1% vs. 92.6%)

- **Efficacy Results:** Efficacy analysis were performed at day 28 using all randomized patients who maintained consent
    - **Primary endpoint:** 11-point WHO Clinical progression ordinal scale (CPS) at day 28. (Note this provides a measure of severity of illness from 0 (not infected), 1-3 (mild disease), 4-5 (hospitalized with moderate disease), 6-9 (hospitalized with severe disease), to 10 (dead)).
        - **Odds of more severe disease at day 28, (ANA vs. placebo): OR 0.37 (95% CI 0.26-0.5), p<0.0001**
        - **Severe respiratory failure by day 28:** 21% vs. 33% (HR 0.66, 95% CI 0.48, 0.92)
        - **Mortality at day 28:** 3.2% vs. 6.9% (HR 0.48, 95% CI 0.22, 1.04), NS
    - **Other endpoints (ANA vs. placebo) by day 28**
        - **Fully recovered, PCR negative** (50.4% vs. 26.5%)
        - **Asymptomatic, PCR positive** (9.9% vs. 3.2%)
        - **Symptomatic, independent** (23% vs. 39.2%
        - **Symptomatic, assistance needed** (6.2% vs. 11.1%)
        - **Hospitalized, off oxygen** (2.2% vs.1.6%)
        - **Hospitalized, nasal/mask oxygen** (2% vs 5.3%)
        - **Need for high-flow oxygen or NIV** (0.2% vs. 0.5%)
        - **Need for MV** (3% vs. 5.8%)
        - **Duration of ICU stay** (10 vs. 14 days)
    - On multivariate analysis, only treatment group was associated with WHO scores at day 28 (use of steroids, severity by WHO classification, BMI > 30 kg/m^2 and country were not significant on multivariate analysis)
    - **Predictors of a favorable response to ANA by labs included at least 2 of the following (CRP > 50 mg/L, neutrophil to lymphocyte ration > 5.5, ferritin > 700 ng/mL and AST > 44 U/L.**

Efficacy Summary:

- The SAVE and SAVE-MORE trials suggest benefit of anakinra in hospitalized patients with severe COVID-19 and elevated suPAR levels. suPAR laboratory testing is not available in the U.S., however. The FDA EUA suggests that certain characteristics may identify a population of patients who are most likely to have a suPAR ≥ 6 ng/mL to be used as a surrogate. They note that patients with at least 3 of 8 of the following criteria are likely to have a suPAR ≥ 6 ng/mL:
    - Age ≥ 75 years
    - Severe pneumonia by WHO criteria
    - SOFA score ≥ 3
    - Neutrophil to lymphocyte ratio ≥ 7
    - Hemoglobin ≥ 10.5 g/dL
    - Medical history of ischemic stroke
    - Blood urea ≥ 50 mg/dL and/or history of renal disease
- The NIH Consensus guidelines commented on ANA on 10/19/21 and stated there was insufficient evidence to recommend for or against ANA for COVID-19.
    - The results of SAVE-MORE were available but the guideline authors pointed out the fact that suPAR measurement is not available in many countries (including the U.S.).
    - Two other trials, CORIMUNO-ANA-1 and REMAP-CAP, did not find benefit with ANA, although these trials were not limited to patients with elevated suPAR levels.
- Currently several treatment options exist that are used in manner similar to ANA, including the JAK inhibitor baricitinib, now FDA approved for treatment of COVID-19, and the IL-6 inhibitor tocilizumab (FDA authorized for COVID-19 under EUA). These are recommended as well as remdesivir or remdesivir with dexamethasone in those who have rapidly increasing oxygen needs and systemic inflammation. Providers should consider the relative benefits, risks and logistics when deciding among treatment options for severe COVID-19. Use of ANA must be consistent with the criteria outlined in the FDA EUA.

Anakinra Safety when used for COVID-19

What safety issues need to be considered when administering ANA for COVID-19?*

- Safety data used to support the FDA EUA are from the SAVE-MORE trials

Contraindications:

- Anakinra is contraindicated in patients with known hypersensitivity to *E.coli* derived proteins, ANA, or any components of the product.

Warnings and precautions

- **Serious infections:** serious have been seen with ANA, in 2% of patients vs. < 1% in clinical trials of RA. Serious infections in SAVE-MORE were noted in 9.1% of ANA vs. 16.4% of placebo patients. In COVID-19, monitor for signs and symptoms of new infections during and after treatment with ANA. There is limited data about the use of ANA in patients with COVID-19 and concomitant active serious infections. Risks and benefits of ANA should be considered. The safety and efficacy of ANA in immunosuppressed patients or in patients with chronic infections.
- **Use with TNF blocking agents:** serious infections were noted more commonly in patients with RA who received ANA with etanercept (7%) vs. etanercept alone (0%). ANA is not recommended for use in combination with TNF blocking agents.
- **Hypersensitivity:** reactions, including anaphylaxis and angioedema have been reported with ANA. If a severe hypersensitivity reaction occurs, ANA should be discontinued, and appropriate therapy initiated.
- **Immunosuppression:** The impact of ANA on development of malignancies in COVID-19 is not known.
- **Immunizations:** in a placebo-controlled trial, no difference was noted in anti-tetanus antibody response with ANA vs. placebo. No data are available about use of ANA with other inactivated vaccines, including COVID-19 vaccines. No data are available on either the effects of live vaccination on secondary transmission of infection by live vaccines in patients on ANA. Avoid use of live vaccines with ANA.
- **Neutropenia:** Patients on ANA may have decrease in neutrophil counts. Patients with ANC < 1500 cells/mm^3 were excluded from SAVE-MORE. Therefore, assess neutrophil counts prior to initiating ANA for COVID and monitor for neutropenia according to current clinical practices.

Adverse events

- Serious treatment emergent adverse events (TEAE) occurred in 16% of ANA vs. 21.7% placebo subjects, including infections (8.4% vs. 15.9%), and pulmonary embolism (1.5% vs. 2.1%). The largest difference in treatment emergent infections was ventilator-associated pneumonia, in 2.2% of ANA vs. 7.9% of placebo patients.
- Selected safety data from the EUA Fact Sheet for Healthcare providers are included in Table 1. Of note, anemia occurred less frequently with ANA than with placebo (14.3% vs 19.6%).

Table 1: Adverse events of ANA vs. placebo in at least 1% of ANA arms and at least 1% more frequently than placebo

Adverse reaction, %	Placebo (n=189)	ANA (n=405)
Transaminase increases	27.5%	30.8%
GGT increased	11.7%	13.8%
Leukopenia	1.1%	3.5%
Neutropenia	0.5%	3.0%
Rash	1.5%	3.7%
Hypernatremia	7.9%	9.6%
Constipation	7.4%	9.1%
Hyperkalemia	7.4%	9.1%
Anxiety	6.3%	8.1%
Hypothermia	4.2%	7.4%
Acute kidney injury	5.2%	6.3%

- **Use in specific populations:**
  - **Pregnancy:** data available from retrospective studies and case reports of use of ANA in pregnant women are insufficient to identify a drug associated risk of maternal or fetal adverse events. In animal studies of rats and rabbits, no evidence of fetal harm was noted at doses up to 25 times the maximum recommended human dose.
  - **Lactation:** No data exist on the presence of ANA in either human or animal milk. The limited clinical data precludes a clear determination of risk of ANA to an infant during lactation.
  - **Geriatric use:** In SAVE-MORE, 42% of patients were aged 65 years or older. No differences in safety or effectiveness were observed versus younger patients, but greater sensitivity of some older patients cannot be ruled out. Because of a higher incidence of infections in the elderly population in general, use caution when treating the elderly.

Will the VA be monitoring for adverse events associated with ANA for COVID-19?

- YES – VA has been monitoring the safety of Anakinra as an off-label use agent in Veteran inpatients with COVID-19 through VA ADERS and through real time surveillance. Given the limited safety data, vigilance in monitoring for adverse events is critical. Physicians, nurses, pharmacists and other healthcare providers should be monitoring patients closely for unusual clinical or laboratory events, record them as per local policy and report them to VA ADERS.
- All ANA related ADEs and medication errors are to be reported as per local policy and to VA ADERS as a MedWatch report (a separate FDA MedWatch report is not required when submitted in VA ADERS). ADEs are reported to VA ADERS using the following link: https://vaww.cmop.med.va.gov/MedSafe_Portal/
- VHA Center for Medication Safety will also be conducting prospective pharmacovigilance to identify potential adverse events and will report those to the FDA .

Other issues

What other things are important to know about ANA or about the FDA EUA

- Information on the FDA Emergency Use Authorization can be found on the FDA website: FDA Emergency Use Authorization Letter for ANA for COVID-19
  Important additional documents include the
  - Fact sheet for healthcare providers 11/8/2022
  - Fact sheet for patients and caregivers 11/8/2022

- **Instructions for Healthcare Providers:**
  - Healthcare providers must communicate to the patient or parent/caregiver/surrogate decision maker (SDM), as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provider a copy of the fact sheet) prior to the patient receiving Anakinra, including:
    - FDA has authorized the emergency use of Anakinra to treat laboratory confirmed COVID-19 in hospitalized adult patients who require supplemental oxygen, and who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR)
    - The patient or parent/caregiver/SDM has the option to accept or refuse ANA.
    - The significant known and potential risks and benefits of ANA and the extent to which such potential benefits and risks are unknown.
    - Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
  - If providing this information will delay the administration of ANA to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after ANA is administered.
  - Provider is responsible for reporting all medication errors and adverse events potentially related to treatment within 7 calendar days of notification and respond to FDA request for information about adverse events.

- **Mandatory requirements for ANA for COVID-19 under Emergency Use Authorization:**
  - VA participation in the EUA program is contingent on the following information being reported to the FDA
    - Patient-specific information on those receiving ANA for COVID-19 (patient name, age, disease manifestation, number of doses administered)
    - Administration information including which lots were received, when they were received, product storage and what outcomes occurred
    - Adverse drug events must be documented in accordance with local policy and placed in the VA ADERS program.

How do I obtain ANA for a patient with COVID-19 at my facility?

- ANA can be obtained via prime vendor orders through normal ordering procedures. In addition to local approval processes; to remain compliant with requirements from the FDA, facilities interested in treating patients with ANA for COVID-19 **must** submit a patient-specific request on the PBM EUA portal**:**
  - Facilities that are eligible to provide EUA products must initiate a request that provides:
    - Patient name, last four of SSN, date of birth, and date of positive COVID-19 test
    - Documentation that the patient meets all criteria listed above
  - Requests that meet all specified criteria will be automatically approved. After approval is obtained, the site may initiate therapy.
  - Upon completion of therapy, the site must provide additional follow-up information including:
    - Which lots were administered
    - When the package arrived
    - Total number of doses given to the patient
    - Dates therapy initiated and completed
    - If and adverse drug events occurred, and if they were documented appropriately (within 7 days of notification)
    - Certification that all information above was completed wholly and accurately (sites may choose to begin adding follow-up information before therapy is completed, and the information will not be considered final until certified).
  - ANY Adverse drug events that occur must be documented in accordance with local policy and ALSO placed in the VA ADERS program (with selection of MedWatch report)
  - Refer to PBM EUA portal for additional help and any updates or changes.

References:

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