# Anakinra (Kineret®)

## A Review of Pertinent Drug Information for SARS-CoV-2

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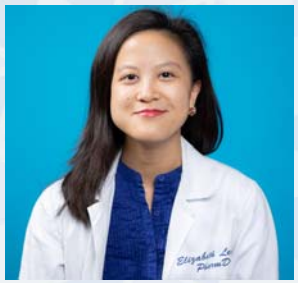

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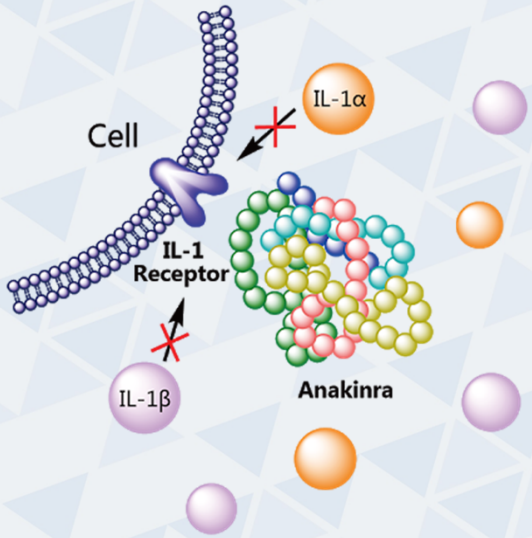
*Data as of October 7, 2020*

# Mechanism of Action

- Recombinant human interleukin-1 receptor antagonist (IL-1Ra)

- Blocks biological activity of IL-1α and IL-1β
  - competitively inhibits IL-1 binding to interleukin-1 type I receptor (IL-1R1)
  - binds to IL-1R1, but does not associate with IL-1 receptor accessory proteins
    - does not have agonist activity
    - does not initiate signaling events

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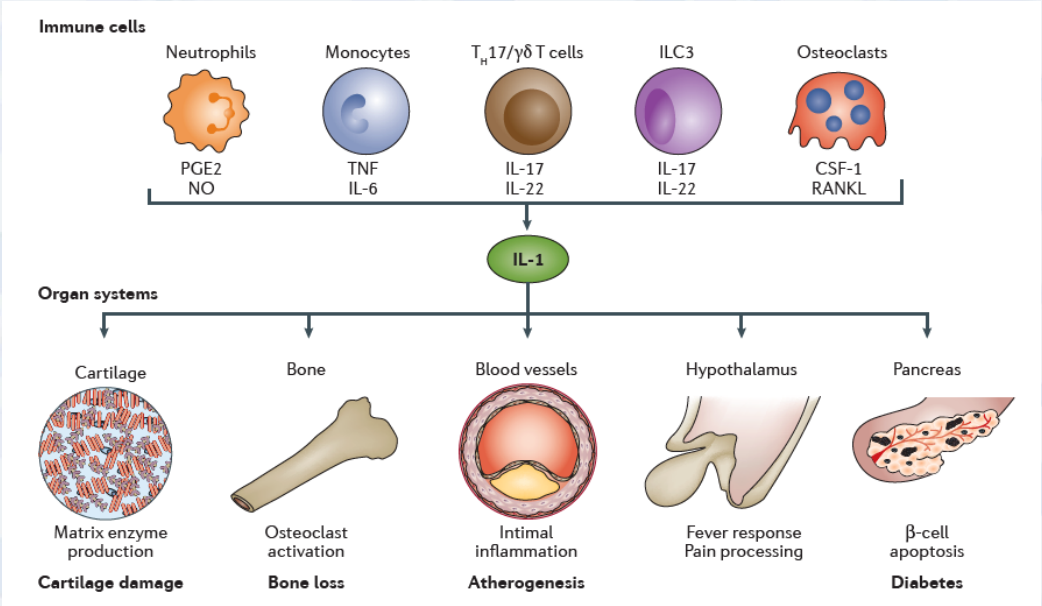
http://182.92.230.50:82/drug/biology/PB0071-Anakinra-structure-01.png
Anakinra Package Insert. Swedish Orphan Biovitrum AB (2018)

# Mechanism of Action

- **Functions of IL-1**
  - IL-1α and IL-1β activated via inflammasome
  - Pro-inflammatory cytokines that mediate many cellular responses
  - ↑ nitric oxide, prostaglandin, adhesion molecules, histamine, thromboxane, etc.

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Schett G, et al. Nat Rev Rheumatol. 2016; 12(1):14-24. doi: 10.1038/nrrheum.2016.166

# Mechanism of Action

- Increased serum levels of pro-inflammatory cytokines associated with pulmonary inflammation and lung damage
  - SARS, MERS-CoV
- COVID-19 patients demonstrated increased levels of cytokines, possibly related to disease severity
  - High levels of cytokines postulated to lead to activated T-helper-1 (Th1) cell response
  - ICU patients demonstrated higher cytokine levels than non-ICU
  - Also secreted Th2 cytokines that suppress inflammation (not in SARS-CoV-2)

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Huang et al. Lancet. 2020; 395: 497–506. doi.org/10.1016/S0140-6736(20)30183-5
Mehta P et al. Lancet. 2020;395:1033-1034. doi.org/10.1016/S0140-6736(20)30628-0

# Dosing

- Initially approved by FDA (2001) and Health Canada (2002)
  - Rheumatoid Arthritis (RA)
    - Adult: 100mg SQ q24h
  - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
    - 8 months and older, >10kg
    - 1-2 mg/kg SQ q24h → maximum daily dose 8 mg/kg
  - Off label uses
    - Familial Mediterranean fever
    - Gout, acute flare
    - Pericarditis, recurrent

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Anakinra Package Insert. Swedish Orphan Biovitrum AB (2018)
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020; April 7, 2020

# Dosing: Special Populations

Limited data

| Population | Recommendation |
|---|---|
| Renal impairment | • CrCL < 30mL/min or end-stage renal disease (ESRD): adjust dosing schedule, ie. consider administering prescribed dose, but given every other day<br>• Hemodialysis: not dialyzable (<2.5%) |
| Hepatic impairment | no dose recommendations |
| Pediatric | weight based dosing has been described |
| Pregnancy | risk/benefit to continue if no safer alternative available to control maternal disease |
| Breastfeeding | endogenous IL-1 Ra can be found in breastmilk |
| Geriatric | no dose adjustment necessary |

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Anakinra [Package Insert]. Swedish Orphan Biovitrum AB (2018)
Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020; April 7, 2020
Götestam Skorpen C, et al. Ann Rheum Dis 2016;75:795–810. doi:10.1136/annrheumdis-2015-208840

# Available Data: Sepsis/Septic Shock

- Phase I[1]
  - single dose IV, up to 10mg/kg
- Phase II in sepsis/septic shock[2]
  - loading dose 100mg IV, followed by 72h infusion (17, 67, or 133 mg/hr)
- Phase IIIs in sepsis/septic shock[3,4]
  - loading dose 100mg IV, followed by 72h infusion (1 or 2mg/kg/hr)
- No reported cases of overdose or severe toxicity attributed to drug

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1. Granowitz E. Cytokine. 1992;4(5):353-360. 2. Fisher et al. Crit Care Med. 1994; 22(1):12-21.
3. Fisher et al. JAMA. 1994;271(23):1836–43. 4. Opal S et al. trial. Crit Care Med. 1997;25(7):1115–24.
Shakoory B et al. CritCareMed. 2016;44(2):275-81. doi: 10.1097/CCM.0000000000001402
Mehta P et al. Lancet. 2020;395:1033-1034. doi.org/10.1016/S0140-6736(20)30628-0

# Safety

- Black box warning
  - Increased incidence of serious infection
  - Allergy/hypersensitivity reaction
    - anaphylaxis, angioedema, urticaria and rash
- Contraindications
  - Hypersensitivity to *E. coli*-derived proteins, anakinra, or any component of the formulation
- Unknown risk of IL-1 blockade on malignancy development

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Anakinra [Package Insert]. Swedish Orphan Biovitrum AB (2018)
Litmanovich A et al. Oncology and Therapy. 2018;6:109-127. https://doi.org/10.1007/s40487-018-0089-z.

# Adverse Drug Reactions

- **>10%:** injection site reactions, headache, vomiting, GI disturbance, arthralgias
- Infections:
  - Mostly upper respiratory and urinary tract infections
  - Serious infections (1.7% vs 1% in placebo)
    - Mainly bacterial: cellulitis, pneumonia, bone/joint
    - Higher incidence of serious infections in asthmatic patients
  - Post-marketing: rare opportunistic bacterial, fungal, mycobacterial, viral
    - All organ systems, whether receiving anakinra alone or with other immunosuppressant agents
- Neutropenia: do not initiate if ANC<$1x10^9$
- Transient liver enzyme elevations, reports of non-infectious hepatitis

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Anakinra [Package Insert]. Swedish Orphan Biovitrum AB (2018)

# Drug-Drug Interactions

| | |
|---|---|
| Immunosuppressants | • potential for additive immunosuppression<br>  • however studied in combination with other DMARD (ie. methotrexate) for RA; risk vs benefit |
| CYP450 substrates | • may decrease concentrations of CYP450 substrates<br>  • IL-1 receptor antagonism may restore/enhance function of CYP450 |
| Vaccinations | • potential increased risk of live vaccines → avoid<br>• potential decreased response to inactivated vaccines |

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Anakinra [Package Insert]. Swedish Orphan Biovitrum AB (2018)

# Clinical Data

- **Systematic Review and Meta-analysis (Aug 2, 2020):**

**TABLE 4:** Included studies investigating other antirheumatic therapies and COVID-19 (n = 3 for anakinra, 4 for IVIG, and 1 for baricitinib)

| Author (citation) | Design (n) | Outcomes and Inference | Bias Assessment* | Direction of Effect† |
|---|---|---|---|---|
| **Anakinra** | | | | |
| **Mortality** | | | | |
| Huet (45) | Cohort (96) | Anakinra associated with lower rate of death (HR 0.3, CI 0.1-0.7) | Some | QS |
| Cavalli (46) | Cohort (52) | Anakinra high dose 5mg/kg BID associated with lower mortality at 21 days (HR 0.2, CI 0.04-0.63) | High | QS |
| **Composite of Intubation and Death** | | | | |
| Huet (45) | Cohort (96) | Anakinra associated with lower rate of composite IMV/death (HR 0.2, CI 0.1-0.5) | Some | + |
| **Escalation of Care (ICU transfer, intubation and mechanical ventilation)** | | | | |
| Huet (45) | Cohort (96) | Anakinra associated with lower rate of invasive mechanical ventilation (HR 0.2, CI 0.1-0.6) | Some | + |
| Cavalli (46) | Cohort (52) | No difference with high dose and IMV free survival at 21 days (HR 0.5, CI 0.2-1.3) | High | + |
| **Clinical Improvement** | | | | |
| Aouba (83) | Case Series (9) | 9 out of 9 patients treated with anakinra improved | High | NA |

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Putman et al (The COVID-19 Global Rheumatology Alliance). Arthritis Rheumatol. 2020 Aug 2;10.1002/art.41469.

# Clinical Data

- **Cavalli (Italy):** retrospective cohort, part of COVID-19 Biobank study (NCT04318366)

| | | |
|---|---|---|
| | **Control** (standard treatment) n=16 | **Study** (standard therapy + anakinra: high dose n=29; low dose n=7) |
| Inclusion (all) | • ≥ 18 years, and admitted to study hospital with COVID-19, moderate-to-severe ARDS, and hyperinflammation:<br>  • SARS-CoV-2 infection confirmed by RT-PCR assay and CXR or CT;<br>  • acute-onset respiratory failure with bilateral infiltrates on CXR/CT, hypoxaemia ($PaO_2$:$FiO_2$ ≤200 mm Hg, with PEEP ≥5cm $H_2O$), and no evidence of left atrial hypertension;<br>  • increase in either serum CRP (≥100 mg/L) or ferritin (≥900 ng/mL) or both | |
| Exclusion (any) | • non-consenting patients<br>• evidence of bacterial infection<br>• already admitted to the ICU for mechanical ventilation<br>• concomitant administration of other anti-inflammatory agents or steroids<br>• concomitantly enrolled in another clinical trial | |
| Cohort | Control (standard treatment)<br>COVID-19 from 3/10-3/17 | **high dose: 5mg/kg IV BID (+taper)** **low dose: 100mg SQ BID**<br>COVID-19 from 3/17-3/27 |

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Standard of Care at study site:
PO hydroxychloroquine 200mg BID x 7-10 days
PO lopinavir/ritonavir 400/100mg BID x 7-10 days
IV antimicrobials (ceftriaxone + azithromycin) – empiric therapy

Cavalli G et al. Lancet Rheumatol 2020 May;2: e325–31.

# Clinical Data

- **Ana-COVID (France):** retrospective cohort study, sponsored by SOBI

| | Historical Control (standard of care) n=44 | Study Group (anakinra) "prospective cohort" n=52 |
|---|---|---|
| Inclusion (all) | • > 18 years, and admitted to study hospital with severe COVID-19-related bilateral pneumonia:<br>• SARS-CoV-2 infection confirmed by RT-PCR assay or a typical aspect on CT scan of the lungs;<br>• bilateral lung infiltrates on a lung CT scan or chest x-ray;<br>• critical lung function: O2 sat ≤ 93% under 6+ L/min of oxygen or O2 sat < 93% on 3 L/min with a saturation on ambient air decreasing by 3% in the previous 24 h | |
| Exclusion (any) | • refusal of the patient to participate<br>• bedridden and near the end of life<br>• respiratory failure explained by an alternative aetiology,<br>• already admitted to the ICU | |
| Cohort | Control (standard treatment + supportive care)<br>Starting 3/18/2020 from all COVID-19 disease | **anakinra 100mg SQ BID x 72h, then 100mg SQ Q24H x7days**<br>+ standard treatment + supportive care (3/24-4/6/2020) |

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Standard of Care at study site:
PO hydroxychloroquine 600mg/day x 10 days
PO azithromycin 250mg/day x 5 days
IV β-lactam antibiotics x 7 days (ceftriaxone or amoxicillin)
thromboembolic prophylaxis

Huet T et al. Lancet Rheumatol. 2020 Jul; 2(7): e393–e400.

# Clinical Trials in Progress - Summary

| Study Name | Study Summary – Currently Recruiting (1) | Posting, Location, Sponsor, Target Enrollment |
|---|---|---|
| Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia **(REMAP-CAP)** **NCT02735707 / 2015-002340-14** | COVID-19 immune modulation domain: no immune modulation, or one of following<br>• **anakinra 300mg IV x1, 100mg IV Q6H x14d (or earlier if extub >24h or ICU d/c)**<br>• IFN-β1a 10mcg IV q24h x 6 days or to ICU discharge (whichever first)<br>• tocilizumab 8mg/kg (max 800mg) IV x1, may repeat x1 in 12-24hrs<br>• sarilumab 400mg IV x1 | First posted 2016<br>**Multiple countries:** Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK. |
| Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection **NCT04324021 / 2020-001167-93** | Phase 2/3, randomized, open-label, parallel group, 3-arm, multicentre<br>• **anakinra 100mg IV q6h x15d**<br>• emapalumab IV Q3days: D1: 6mg/kg IV, D4, 7, 10, 13: 3mg/kg IV<br>• standard of care | First posted Mar 27, 2020<br>SOBI: USA + Italy<br>(goal #54) |
| Treatment of COVID-19 Patients With Anti-interleukin Drugs **(COV-AID)** **NCT04330638 / 2020-001500-41** | Prospective, randomized, factorial design, open-label<br>• **anakinra 100mg SQ Q24H x28d or discharge (whichever first)** • usual care<br>• siltuximab 11mg/kg IV x1 • tocilizumab 8mg/kg IV x1 (max 800mg)<br>• anakinra + situximab • anakinra + tocilizumab | First posted April 1, 2020<br>Belgium<br>(goal #342) |
| Efficiency in Management of Organ Dysfunction with Infection by the Novel SARS-CoV-2 Virus through a personalized immunotherapy approach **(ESCAPE)** **NCT04339712 / 2020-001039-29** | Open label exploratory, non-randomized, non-controlled, unblinded<br>• **anakinra 200mg IV Q8H x7d**<br>• tocilizumab 8mg/kg IV x1 (maximum 800mg) | First Posted April 9, 2020<br>Hellenic Institute for the Study of Sepsis, Greece<br>(goal #40) |

REMAP-CAP. https://www.remapcap.org/
More information available at: clinicaltrials.gov

| Study Name | Study Summary – Currently Recruiting (2) | Posting, Location, Target Enrollment |
|---|---|---|
| suPAR-guided Anakinra for Validation of the Risk and Management of Respiratory Failure by COVID-19 **(SAVE)** **NCT04357366 / 2020-001466-11** | Single group, open label, to prevent progression if biomarker is elevated<br>• **anakinra 100mg SQ Q24H x10d** + SMX/TMP 1 SS PO Q24H x10d | First posted April 22, 2020<br>Greece (goal #100) |
| Early Treatment of Cytokine Storm Syndrome in Covid-19 **NCT04362111** | Prospective, randomized, parallel, triple blind study<br>• **anakinra 100mg SQ Q6H x10d** (may decrease to Q12H in last 5d)<br>• placebo | First posted April 24, 2020<br>Univ of Alabama Birmingham (goal #30) |
| Anakinra for COVID-19 Respiratory Symptoms **(ANACONDA)** **NCT04364009 / 2020-001734-36** | Phase 3, randomized, parallel, open label study<br>• **anakinra 100mg IV Q6H on D1-3, 100mg IV Q12H on D4-10** + SOC<br>• standard of care (SOC) | First posted April 27, 2020<br>SOBI: CHRU, Tours, France (goal #240) |
| Clinical-epidemiological Characterization of COVID-19 Disease in Hospitalized Older Adults **(COVID-AGE)** **NCT04362943** | Retrospective clinical-epidemiological study to characterize outcomes of COVID-19 disease in those treated with anakinra or baricitinib | First posted April 27, 2020<br>Albacete, Spain (goal #576) |
| Plasma Exchange in Patients With COVID-19 Disease and Invasive Mechanical Ventilation **(REP-COVID)** **NCT04374539** | Mainly a Plasma Exchange RCT, where "standard of care" includes:<br>• **anakinra 200mg SQ Q12H on D1, 200mg SQ Q24H on D2-3** + HCQ x5d + LPV/RTV x7d + azithromycin x5d + tocilizumab + methylprednisolone x6d | First posted May 5, 2020<br>Barcelona, Spain (goal #116) |
| Efficacy and Safety of Angiotensin II Use in COVID-19 Patients With Acute Respiratory Distress Syndrome **(ACES)** **NCT04408326** | Retrospective observational case control study to characterize putcomes of COVID-19 disease in ICU patients who received anakinra or angiotensin II | First posted May 29, 2020<br>London, UK (goal #50) |
| A Study in Patients With COVID-19 and Respiratory Distress Not Requiring Mechanical Ventilation: The Immunomodulation-CoV Assessment **(ImmCoVA)** Study **NCT04412291 / 2020-001748-24** | Randomized, controlled, single-center open-label trial in severe COVID19<br>• **anakinra 100mg IV Q6H x7d** + SOC<br>• tocilizumab 8mg/kg IV x1 (max 800mg), may repeat x1 if > 48hrs + SOC<br>• standard of care (acetaminophen + antibiotics x7d + VTE prophylaxis) | First posted June 2, 2020<br>Karolinska Hospital, Sweden (goal #120) |
| Clinical Trial of the Use of Anakinra in Cytokine Storm Syndrome Secondary to Covid-19 **(ANA-COVID-GEAS)** **NCT04443881 / 2020-001825-29** | Phase 2/3, randomized, parallel open label trial<br>• **anakinra 100mg IV Q6H x15d maximum** + SOC<br>• standard of care (SOC) | First posted June 23, 2020<br>Barcelona, Spain goal #180) |

More information available at: clinicaltrials.gov

| Study Name | Study Summary – Not Recruiting (1) | Posting, Location, Sponsor, Target Enrollment |
|---|---|---|
| Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients **(CORIMUNO-19) France** NCT04324047 / 2020-001246-18 | Observational: open-label, parallel group – ? no doses/durations on trial listing<br>• **anakinra IV (100mg/0.67mL** syringe) • hydroxychloroquine 200mg<br>• sarilumab IV (200mg syringe) • azithromycin 250mg PO<br>• tocilizumab IV (20mg/mL, 20mL) • standard of care<br>• eculizumab IV (300mg) | First posted March 27, 2020<br>Paris, France<br>(goal #500-1000) |
| → Trial Evaluating Efficacy Of Anakinra In Patients With Covid-19 Infection **(CORIMUNO-ANA) NCT04341584** | Phase 2, randomized, parallel, open label study, nested in CORIMUNO-19<br>• **anakinra 200mg IV BID on D1-3, 100mg IV BID on D4, 100mg IV Q24H on D5.** may extend 200mg IV BID on D4-6, 100mg IV BID on D7, 100mg IV Q24H on D8 | First posted April 10, 2020<br>Paris, France<br>(goal #240) |
| Efficacy of Intravenous Anakinra and Ruxolitinib During COVID-19 Inflammation **(JAKINKOV) NCT04366232 / 2020-001963-10** | Phase 2, randomized, parallel, open label, 2 arms (gradual strategy by clinical stage)<br>• **anakinra 300mg IV Q24H x5d** with dose tapering<br>• **anakinra 300mg IV Q24H (max 14d)** + ruxolitinib 5mg PO BID (max 28d)<br>• standard of care | First posted April 28, 2020<br>Toulon La Seyne sur Mer, France<br>(goal #54) |
| A Trial Using Anakinra or Tocilizumab Alone or in Association With Ruxolitinib in Severe Stage 2b and 3 of COVID19-associated Disease **(INFLAMMACOV) NCT04424056 / 2020-001754-21** | Prospective, randomized, parallel, open label study of combinations by disease stage<br>• anakinra +/- ruxolitinib (stage 2b/3) • anakinra + ruxolitinib (adv stage 3)<br>• tocilizumab +/- ruxolitinib (stages 2b/3) • tocilizumab + ruxolitinib (adv stage 3)<br>• standard of care | First posted June 9, 2020<br>Marseille, France<br>(goal #216) |
| SCIL-1Ra in COVID-19 Feasibility & PK/PD **(SCIL_COV19) NCT04462757 / 2020-001636-95** | Prospective, randomized, parallel, open label PK study of IV/SQ high/low dose<br>• **anakinra 100mg SQ BID** (min 8hrs, max 16hrs between doses) **x14d** (or ICU d/c)<br>• **anakinra 100mg IV Q6H x14d** (or to ICU d/c) | First posted July 8, 2020<br>University of Manchester<br>(goal #5-40) |

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More information available at: clinicaltrials.gov

# Clinical Pearls

- **Who?**
  - Criteria for use in resource-limited settings *
    - Identifying and categorizing MAS, CRS (CTCAE criteria, Lee or Penn Scales, H-Score)
    - Availability and turn-around time of inflammatory biomarkers
  - Rule out latent TB – utility in critically ill patients
  - Monitor other drugs (i.e. tacrolimus)
- **What?**
  - Dosing regimens are highly variable, ? taper, ? biomarkers
- **When?**
  - Optimal timing of administration in course of disease
- **How?**
  - IV vs SQ: only SQ formulation available, light sensitive, ? stability/compatibility

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* Henderson LA et al. Arthritis & Rheumatology. 2020, pp 1–15. doi 10.1002/art.41454 , or https://www.rheumatology.org/Portals/0/Files/ACR-COVID-19-Clinical-Guidance-Summary-MIS-C-Hyperinflammation.pdf

# Summary

- Anakinra is a recombinant human IL-1 receptor antagonist (IL-1Ra)
- Currently approved to treat RA and NOMID
- Since CRS/MAS may be involved in the pathogenesis of SARS-CoV-2, anakinra is under investigation for this indication
- Studied in sepsis, and limited clinical data is available for SARS-CoV2
- Safety profile is similar to other immunomodulatory therapies under consideration for SARS-CoV-2
- Currently, the role of targeted immunomodulatory therapies for treatment of SARS-CoV-2 infection is not well defined

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## A Review of Pertinent Drug Information for SARS-CoV-2

**Beth Leung, PharmD, MSCI, BCPS AQID**
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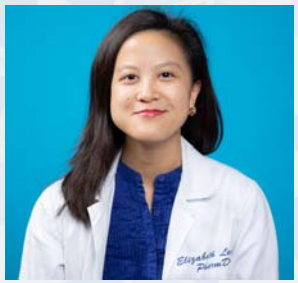

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*Data as of October 7, 2020*