Anakinra (Kineret®)

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

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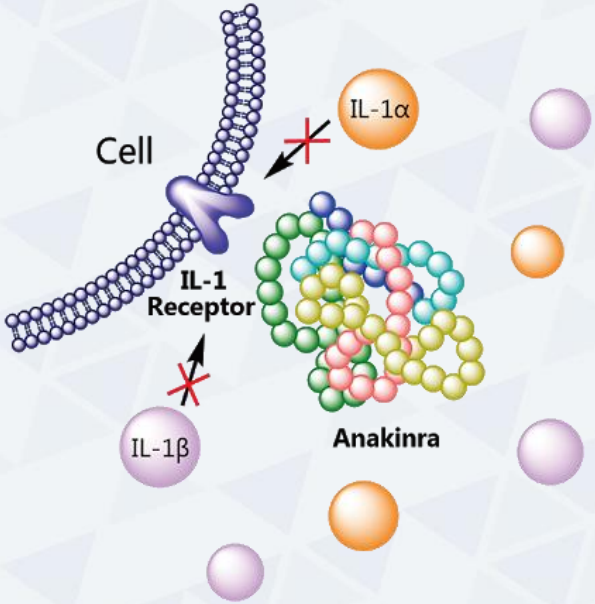
Data as of April 13, 2020

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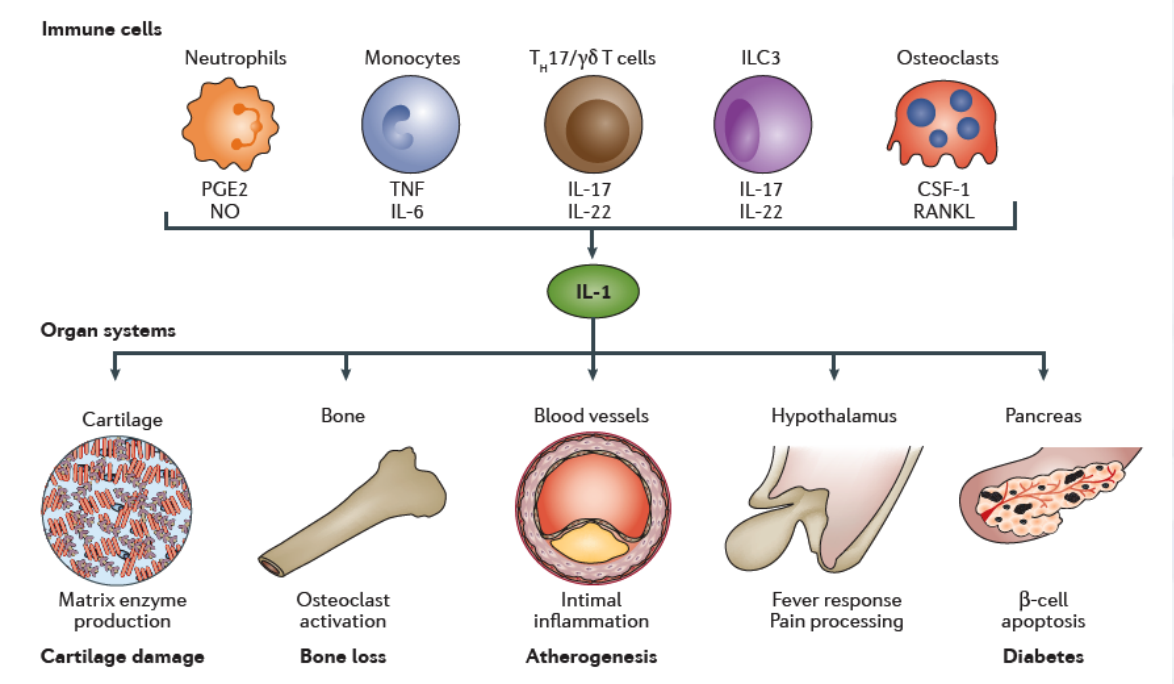
http://182.92.230.50:82/drug/biology/PB0071-Anakinra-structure-01.png
Anakinra Package Insert. Swedish Orphan Biovitrum AB (2018)

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

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 • 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

Limited data

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

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Clinical Trials in Progress

Study Name	Study Interventions	Study Enrollment & Outcomes
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia **(REMAP-CAP)** **Multiple countries:** Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK. **(NCT02735707 – recruiting)**	Bayesian adaptive platform trial - multiple existing domains for CAP https://www.remapcap.org/protocol-documents <u>COVID-19 immune modulation domain</u> • **anakinra 300mg IV Q24h x 14 days or until extubated >24h** • IFN-β1a 10mcg IV q24h x 6 days or until ICU discharge (whichever first) • no immune modulation	Target enrollment 6800 Age >18 yo, ICU patients @ 90 days: all cause mortality @ 21d days: alive and ICU free days

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

Clinical Trials in Progress

Study Name	Study Interventions	Study Enrollment & Outcomes
Recruiting Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection **Italy** (NCT04324021 – recruiting)	Phase 2/3, randomized, open-label, parallel group, 3-arm, multicentre • **anakinra 100mg IV q6h x 15 days** • emapalumab IV Q3days: D1: 6mg/kg IV, D4, 7, 10, 13: 3mg/kg IV • standard of care	Target enrollment: 54 Age 30-79 yo @ 15 days: treatment success (not requiring ventilation or ECMO)
Treatment of COVID-19 Patients With Anti-interleukin Drugs **(COV-AID)** **Belgium** (NCT04330638 – recruiting)	Prospective, randomized, factorial design, interventional study • **anakinra 100mg SQ x 28 days or discharge (whichever first)** • siltuximab 11mg/kg IV x1 dose • usual care • tocilizumab 8mg/kg IV x1 (maximum 800mg) • anakinra + situximab • anakinra + tocilizumab	Target enrollment: 342 Age 8-80 yo @ 15 days: time to clinical improvement or discharge from hospital
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 – recruiting)	Observational: open-label, parallel group – ? no doses/durations • **anakinra IV (100mg/0.67mL** syringe) • hydroxychloroquine 200mg • sarilumab IV (200mg syringe) • azithromycin 250mg PO • tocilizumab IV (20mg/mL, 20mL) • standard of care • eculizumab IV (300mg)	Target enrollment: 500-1000 Age >18 yo @ 14 days/ICU: extubation >48h @ 14 days/Non-ICU: survival without ventilator
Efficiency in Management of Organ Dysfunction with Infection by the Novel SARS-CoV-2 Virus through a personalized immunotherapy approach **(ESCAPE)** **Greece** (NCT04339712 / 2020-001039-29 – ongoing)	Open label exploratory, non-randomized, non-controlled, unblinded • **anakinra 200mg IV Q8H x 7 days** • tocilizumab 8mg/kg IV x1 (maximum 800mg)	Target enrollment: 20 Age >18 yo @ 8 days: composite endpoint (>25% decrease in SOFA, clinical improvement of lung involvement

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 (IV vs SQ)
- **When?**
  - Optimal timing of administration

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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, however no SARS-CoV2 clinical data is available
- 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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