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
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.
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)
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
### Dosing: Special Populations

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

Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2020; April 7, 2020
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

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
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

**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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<tr>
<th>Study Name</th>
<th>Study Interventions</th>
<th>Study Enrollment &amp; Outcomes</th>
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| Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) | Bayesian adaptive platform trial - multiple existing domains for CAP  
https://www.remapcap.org/protocol-documents  
COVID-19 immune modulation domain  
• 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 |

**Multiple countries:** Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK.  
(NCT02735707 – recruiting)
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<tr>
<td>Recruiting Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyperinflammation and Respiratory Distress in Patients With COVID-19 Infection Italy</td>
<td>Phase 2/3, randomized, open-label, parallel group, 3-arm, multicentre • <strong>anakinra 100mg IV q6h x 15 days</strong> • <strong>emapalumab IV Q3days: D1: 6mg/kg IV, D4, 7, 10, 13: 3mg/kg IV</strong> • standard of care</td>
<td>Target enrollment: 54 Age 30-79 yo @ 15 days: treatment success (not requiring ventilation or ECMO)</td>
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<tr>
<td>Treatment of COVID-19 Patients With Anti-interleukin Drugs (COV-AID) Belgium</td>
<td>Prospective, randomized, factorial design, interventional study • <strong>anakinra 100mg SQ x 28 days or discharge (whichever first)</strong> • siltuximab 11mg/kg IV x1 dose • tocilizumab 8mg/kg IV x1 (maximum 800mg) • anakinra + situximab • anakinra + tocilizumab</td>
<td>Target enrollment: 342 Age 8-80 yo @ 15 days: time to clinical improvement or discharge from hospital</td>
</tr>
<tr>
<td>Cohort Multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients (CORIMUNO-19) France</td>
<td>Observational: open-label, parallel group – ? no doses/durations • <strong>anakinra IV (100mg/0.67mL syringe)</strong> • sarilumab IV (200mg syringe) • tocilizumab IV (20mg/mL, 20mL) • eculizumab IV (300mg)</td>
<td>Target enrollment: 500-1000 Age &gt;18 yo @ 14 days/ICU: extubation &gt;48h @ 14 days/Non-ICU: survival without ventilator</td>
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<tr>
<td>Efficiency in Management of Organ Dysfunction with Infection by the Novel SARS-CoV-2 Virus through a personalized immunotherapy approach (ESCAPE) Greece</td>
<td>Open label exploratory, non-randomized, non-controlled, unblinded • <strong>anakinra 200mg IV Q8H x 7 days</strong> • tocilizumab 8mg/kg IV x1 (maximum 800mg)</td>
<td>Target enrollment: 20 Age &gt;18 yo @ 8 days: composite endpoint (&gt;25% decrease in SOFA, clinical improvement of lung involvement)</td>
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</table>
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
• 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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