Anakinra (Kineret®)

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

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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
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.

• 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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</table>
| Renal impairment | • CrCL < 30mL/min or end-stage renal disease (ESRD): adjust dosing schedule, i.e. consider administering prescribed dose, but given every other day  
• Hemodialysis: not dialyzable (<2.5%) |
Available Data: Sepsis/Septic Shock

• Phase I¹
  • single dose IV, up to 10mg/kg

• Phase II in sepsis/septic shock²
  • loading dose 100mg IV, followed by 72h infusion (17, 67, or 133 mg/hr)

• Phase IIIs in sepsis/septic shock³,⁴
  • 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<1x10⁹
• 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

Clinical Data

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

<table>
<thead>
<tr>
<th>Author (citation)</th>
<th>Design (n)</th>
<th>Outcomes and Inference</th>
<th>Bias Assessment*</th>
<th>Direction of Effect†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td>Anakinra associated with lower rate of death (HR 0.3, CI 0.1-0.7)</td>
<td>Some</td>
<td>QS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anakinra high dose 5mg/kg BD associated with lower mortality at 21 days (HR 0.2, CI 0.04-0.63)</td>
<td>High</td>
<td>QS</td>
</tr>
<tr>
<td>Composite of intubation and Death</td>
<td></td>
<td>Anakinra associated with lower rate of composite IMV/death (HR 0.2, CI 0.1-0.6)</td>
<td>Somewhat</td>
<td>+</td>
</tr>
<tr>
<td>Escalation of Care (ICU transfer, intubation and mechanical ventilation)</td>
<td></td>
<td>Anakinra associated with lower rate of invasive mechanical ventilation (HR 0.2, CI 0.1-0.6)</td>
<td>Somewhat</td>
<td>+</td>
</tr>
<tr>
<td>Cavalli (46)</td>
<td>Cohort (52)</td>
<td>No difference with high dose and IMV free survival at 21 days (HR 0.5, CI 0.2-1.3)</td>
<td>High</td>
<td>+</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>Acouba (83)</td>
<td>0 out of 0 patients treated with anakinra improved</td>
<td>High</td>
<td>NA</td>
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</table>

### Clinical Data

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

<table>
<thead>
<tr>
<th>Inclusion (all)</th>
<th>Control (standard treatment) n=16</th>
<th>Study (standard therapy + anakinra: high dose n=29; low dose n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥ 18 years, and admitted to study hospital with COVID-19, moderate-to-severe ARDS, and hyperinflammation:</td>
<td>• SARS-CoV-2 infection confirmed by RT-PCR assay and CXR or CT;</td>
<td>• concomitant administration of other anti-inflammatory agents or steroids</td>
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<td></td>
<td>• acute-onset respiratory failure with bilateral infiltrates on CXR/CT, hypoxaemia (PaO₂:FiO₂ ≤200 mm Hg, with PEEP ≥5 cm H₂O), and no evidence of left atrial hypertension;</td>
<td>• concomitantly enrolled in another clinical trial</td>
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<tr>
<td></td>
<td>• increase in either serum CRP (≥100 mg/L) or ferritin (≥900 ng/mL) or both</td>
<td></td>
</tr>
<tr>
<td>Exclusion (any)</td>
<td>• non-consenting patients</td>
<td>• concomitant administration of other anti-inflammatory agents or steroids</td>
</tr>
<tr>
<td></td>
<td>• evidence of bacterial infection</td>
<td>• concomitantly enrolled in another clinical trial</td>
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<tr>
<td></td>
<td>• already admitted to the ICU for mechanical ventilation</td>
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**Cohort**

- Control (standard treatment)
  - COVID-19 from 3/10-3/17

- Study (standard therapy + anakinra)
  - High dose: 5mg/kg IV BID (+taper)
  - Low dose: 100mg SQ BID

**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

# Clinical Data

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

<table>
<thead>
<tr>
<th>Inclusion (all)</th>
<th>Historical Control (standard of care) n=44</th>
<th>Study Group (anakinra) “prospective cohort” n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 18 years, and admitted to study hospital with severe COVID-19-related bilateral pneumonia:</td>
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<tr>
<td>• SARS-CoV-2 infection confirmed by RT-PCR assay or a typical aspect on CT scan of the lungs;</td>
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<tr>
<td>• bilateral lung infiltrates on a lung CT scan or chest x-ray;</td>
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<tr>
<td>• critical lung function: O2 sat ≤ 93% under 6+ L/min of oxygen or O2 sat &lt; 93% on 3 L/min with a saturation on ambient air decreasing by 3% in the previous 24 h</td>
<td></td>
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</table>

| Exclusion (any) | | |
|-----------------|-------------------------------------------------|
| refusal of the patient to participate | respiratory failure explained by an alternative aetiology, |
| bedridden and near the end of life | already admitted to the ICU |

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Control (standard treatment + supportive care)</th>
<th>anakinra 100mg SQ BID x 72h, then 100mg SQ Q24H x7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting 3/18/2020 from all COVID-19 disease</td>
<td>+ standard treatment + supportive care (3/24-4/6/2020)</td>
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</table>

**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

# Clinical Trials in Progress - Summary

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Summary – Currently Recruiting (1)</th>
<th>Posting, Location, Sponsor, Target Enrollment</th>
</tr>
</thead>
</table>
| 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  
  • anakinra 300mg IV x1, 100mg IV Q6H x14d (or earlier if extub >24h or ICU d/c)  
  • IFN-$
\beta$1a 10mcg IV q24h x 6 days or to ICU discharge (whichever first)  
  • tocilizumab 8mg/kg (max 800mg) IV x1, may repeat x1 in 12-24hrs  
  • sarilumab 400mg IV x1 | First posted 2016  
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  
  • anakinra 100mg IV q6h x15d  
  • emapalumab IV Q3days: D1: 6mg/kg IV, D4, 7, 10, 13: 3mg/kg IV  
  • standard of care | First posted Mar 27, 2020  
SOBI: USA + Italy (goal #54) |
| Treatment of COVID-19 Patients With Anti-interleukin Drugs (COV-AID) NCT04330638 / 2020-001500-41 | Prospective, randomized, factorial design, open-label  
  • anakinra 100mg SQ Q24H x28d or discharge (whichever first)  
  • siltuximab 11mg/kg IV x1  
  • anakinra + siltuximab  
  • tocilizumab 8mg/kg IV x1 (max 800mg)  
  • anakinra + tocilizumab  
  • usual care | First posted April 1, 2020  
Belgium (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  
  • anakinra 200mg IV Q8H x7d  
  • tocilizumab 8mg/kg IV x1 (maximum 800mg) | First Posted April 9, 2020  
Hellenic Institute for the Study of Sepsis, Greece (goal #40) |

REMAP-CAP. [https://www.remapcap.org/](https://www.remapcap.org/)
More information available at: clinicaltrials.gov
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Summary – Currently Recruiting (2)</th>
<th>Posting, Location, Target Enrollment</th>
</tr>
</thead>
</table>
| 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  
• anakinra 100mg SQ Q24H x10d + SMX/TMP 1 SS PO Q24H x10d | First posted April 22, 2020  
Greece (goal #100) |
| Early Treatment of Cytokine Storm Syndrome in Covid-19 NCT04362111         | Prospective, randomized, parallel, triple blind study  
• anakinra 100mg SQ Q6H x10d (may decrease to Q12H in last 5d)  
• placebo | First posted April 24, 2020  
Univ of Alabama Birmingham (goal #30) |
| Anakinra for COVID-19 Respiratory Symptoms (ANACONDA) NCT04364009 / 2020-001734-36 | Phase 3, randomized, parallel, open label study  
• anakinra 100mg IV Q6H on D1-3, 100mg IV Q12H on D4-10 + SOC  
• standard of care (SOC) | First posted April 27, 2020  
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  
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:  
• 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  
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 outcomes of COVID-19 disease in ICU patients who received anakinra or angiotensin II | First posted May 29, 2020  
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  
• anakinra 100mg IV Q6H x7d + SOC  
• tocilizumab 8mg/kg IV x1 (max 800mg), may repeat x1 if > 48hrs + SOC  
• standard of care (acetaminophen + antibiotics x7d + VTE prophylaxis) | First posted June 2, 2020  
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  
• anakinra 100mg IV Q6H x15d maximum + SOC  
• standard of care (SOC) | First posted June 23, 2020  
Barcelona, Spain (goal #180) |

More information available at: clinicaltrials.gov
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Summary – <strong>Not Recruiting (1)</strong></th>
<th>Posting, Location, Sponsor, Target Enrollment</th>
</tr>
</thead>
</table>
| 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  
  - anakinra IV (100mg/0.67mL syringe)  
  - sarilumab IV (200mg syringe)  
  - tocilizumab IV (20mg/mL, 20mL)  
  - eculizumab IV (300mg)  
  - hydroxychloroquine 200mg  
  - azithromycin 250mg PO  
  - standard of care | First posted March 27, 2020 Paris, France (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  
  - 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 Paris, France (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)  
  - anakinra 300mg IV Q24H x5d with dose tapering  
  - anakinra 300mg IV Q24H (max 14d) + ruxolitinib 5mg PO BID (max 28d)  
  - standard of care | First posted April 28, 2020 Toulon La Seyne sur Mer, France (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  
  - anakinra +/- ruxolitinib (stage 2b/3)  
  - tocilizumab +/- ruxolitinib (stages 2b/3)  
  - standard of care | First posted June 9, 2020 Marseille, France (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  
  - anakinra 100mg SQ BID (min 8hrs, max 16hrs between doses) x14d (or ICU d/c)  
  - anakinra 100mg SQ BID (min 8hrs, max 16hrs between doses) x14d (or ICU d/c)  
  - tocilizumab +/- ruxolitinib (adv stage 3)  
  - standard of care | First posted July 8, 2020 University of Manchester (goal #5-40) |

*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

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

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