Immunomodulators in COVID: Data to date

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Appreciate many people for contributing opinions, preprints, time. (Stan Deresinski, Upi Singh, Will Alegria, David Ha, Beth Martin, Angela Rogers, Tamiko Katsumoto, Mark Genovese, Joe Levitt, David Miklos)

Biomarkers of severity:

- Viral load by respiratory viral PCR. Higher in more severe disease, higher in elderly patients.
- IL-6, CRP. CRP is a fairly reliable marker of IL-6 activity, and is easy/automated and cheap. No clear utility to sending IL-6 levels often if you have CRP. Send out. Elevation in IL-6 may predict severe disease.
- D-dimer: elevation may also predict severe disease
- NLR (neutrophil:lymphocyte ratio), as well as high ANC, low ALC
- Ferritin
- Procalcitonin? Although usually normal, when it is elevated, may bode poorly.
- LDH
- Possibly troponin, markers of cardiac damage / inflammation

Inflammatory markers are elevated in severe COVID. (Sicker patients do worse.)

- How much is appropriate response to high viral load, and how much is inappropriate inflammatory cascade?
  - Reports of “cytokine release syndrome” and “secondary HLH”: are these labels accurate?
    Answer: don’t know, can’t distinguish right now. Per Beth Martin, cytokine profiles don’t really that closely resemble classical HLH; don’t use H score or MD calc website. IL-6 levels in COVID much lower than in sepsis and CAR-T induced cytokine release syndrome. Ferritins confounded by myositis (check CPK) and mild hepatitis. Coagulopathy not typical of HLH.
- Does it make sense to block inflammation without blocking viral replication?
  - Blocking inflammation in sepsis studies have not borne out (e.g. TNFa inhibitors).
    - ?Subgroup analysis -- possible role of anakinra?

For all of these agents: not enough data to recommend their use outside of clinical trials. Avoid if known bacterial or fungal infection, baseline immunosuppression, pregnancy.

Off-label use of any of the FDA approved agents discussed herein requires approval of Pharmacy after discussion with Infectious Diseases and Pulmonary Medicine.

<table>
<thead>
<tr>
<th>anti-IL-6</th>
<th>Tocilizumab (IL-6R), sarilumab (IL-6R), siltuximab (IL-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 activity</td>
<td>Induction of acute phase reactants, generation of fever, tissue repair, angiogenesis, hematopoiesis. Increases CRP, fibrinogen, hepcidin. Reduces albumin synthesis. Neutrophil</td>
</tr>
</tbody>
</table>
chemotaxis. T cell survival and differentiation. Suppresses T regs. Promotes antibody production, plasmablast survival. Known to be elevated in ARDS and predicts poor outcomes.

<table>
<thead>
<tr>
<th>COVID rationale</th>
<th>Elevated IL-6 in several COVID studies esp in severe disease. Levels are lower than typically seen in sepsis and ARDS. Not useful marker of response in rheumatologic disease.</th>
</tr>
</thead>
</table>
| Data in COVID   | 1. Tocilizumab: Xu et al. (China)  
2. Siltuximab: Gritti et al. (Italy)  
3. Tocilizumab: Luo et al. (China)  
4. Tocilizumab: Sciascia et al. (Italy)  
5. Tocilizumab (and 2 anakinra): Quartuccio et al. (Italy) |
| Clinical trials | Tocilizumab RCT (Genentech): enrolling at SHC  
Sarilumab RCT (Regeneron): enrollment completed  
Siltuximab RCT in Spain |
| Notes           | Avoid if already neutropenic.  
Will cause immediate neutropenia (may not be functional)  
Anecdotally, once ARDS sets up, probably not going to help.  
?Role in myocarditis  
?Role in patients with high IL-6 levels at baseline (Castleman’s, myeloma, CAEBV, sarcoid, hx of HLH)  
Once on anti-IL-6, CRP and fever will predictably decrease. Just means the drug is binding its target. (IL-6 not reliable after dosing.). |

  - Was also the only cytokine they reported.  
  - Sicker patients do worse?
Xu et al. ([https://www.ncbi.nlm.nih.gov/pubmed/32350134](https://www.ncbi.nlm.nih.gov/pubmed/32350134) in PNAS, May 1): Tocilizumab, single arm. n=21 pts w/ “severe disease” (tachypnea or hypoxemia) or “critical disease” (invasive or noninvasive vent, shock, other organ failure). No control group. All also on lopinavir and methylprednisolone.
- >80% males. 3 were “critical” and the rest “severe”
- CRP elevated in all. Most lymphopenic, normal PCT. No details on IL-6 except elevated in some.
- Outcomes:
  - All defervesced 1d after. One weaned off vent 1d later.
  - O2 requirement decreased in 15/20 (timeframe not specified)
  - 19 had improvement of radiographic findings (timeframe not specified)
  - 19 discharged including 2 critical patients.
  - Average time from tocilizumab dose to discharge ~13 days. (a bit longer than 11-day average length of hospitalization in Zhou et al. Lancet)

- No exclusion or inclusion criteria. Median age 64y, 86% men.
- CRP median 23.4. IL-6 elevated in 19/21 (median 139.5)
- All 21 pts required CPAP or NIV. (sicker than toci study pts).
- Median f/u 8 days.
Outcomes:
- 33% improved (off CPAP/NIV), 43% stable (still on CPAP/NIV), 24% worsened (intubated or died).
- CRP normalized by day 5 (not surprising or terribly informative).
- case-control study and longer f/u to be published per Will.

  - 15 pts, retrospective. No control group.
  - 8 also methylpred.
  - 2 moderate, 6 serious, 7 critical. *didn’t define severity classifications (refer to Natl Health comm of china)*
  - Toci dose range 80-600 mg per dose. 5 got 2+ doses.
  - M 12, F 3. median age 73.
  - Only included if CRP elevated if > 5 and IL-6 elevated if > 7. If below those levels, then excluded from analysis, called “dropout.”

Results:
- CRP down in all. sIL-6 spiked then declined.
- of 7 critical patients, 4 got single dose. Of those 4, 3 died, and the 4th got worse.
  - 4 who failed tx: persistent and dramatic increase of IL-6.
- The rest made stabilized.
- Really doesn’t make the case for steroids + TCZ. of the 4 critically pts who got both, 3 died, and 1 deteriorated.
- Doesn’t seem to have a role in critically ill pts. ?Role in moderate or severe disease, but only followed for a week.
- They conclude that should give more than one dose if not working??
- (this may have been the classification of severity, but they didn’t state explicitly -- got this from: https://pubs.rsna.org/doi/full/10.1148/radiol.2020200490)

### Table 2: Criteria for Clinical Severity of Confirmed Coronavirus Disease 2019 (COVID-19) Pneumonia

<table>
<thead>
<tr>
<th>Types</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Mild</td>
<td>Mild clinical symptoms [fever &lt;38°C (quelled without treatment), with or without cough, no dyspnea, no gasping, no chronic disease] No imaging findings of pneumonia</td>
</tr>
<tr>
<td>Moderate</td>
<td>Fever, respiratory symptoms, imaging findings of pneumonia</td>
</tr>
</tbody>
</table>
| Severe  | Meet any of the followings:
|         | a. Respiratory distress, RR ≥30 times/min                                |
|         | b. SpO₂ <93% at rest                                                    |
|         | c. PaO₂/FiO₂ ≤ 300 mmHg                                                 |
|         | * Patients showing a rapid progression (>50%) on CT imaging within 24-48 hours should be managed as severe (added in the trial sixth edition) |
| Critical| Meet any of the followings:
|         | a. Respiratory failure, need mechanical assistance                       |
|         | b. Shock                                                                 |
|         | c. “Extra pulmonary” organ failure, intensive care unit is needed       |

Data from Refs. 13,34-39

Abbreviations: RR: respiratory rate; SpO₂: oxygen saturation; PaO₂: partial pressure of oxygen; FIO₂: fraction of inspired oxygen
Cautionary tale of two cases COVID tx w/ tocilizumab. Both progressed to sHLH anyway, and one developed viral myocarditis.

  
  - Inclusion criteria: pcr+, O2 sat <93% or PaO2/FiO2 <300 mmHg, laboratory derangements of >3 of CRP >10x nl, ferritin >1000 ng/ml, D-dimer >10x nl, LDH >2x ULN. Measured IL-6.
  - Received toci IV or SC, 1-2 doses (determined by drug availability)
  - Data collected at days 1, 2, 7, 14. Primary endpoint = safety.
  - 63 pts (56M, age 62.6+/−12.5y). 5 (8%) on invasive mechanical ventilation from admission. Followed at least 14d after admission.
    - All on antivirals (LPV/r 71%, DRV/cobi 29%)
    - 40% febrile on admission. Resolved after TCZ. Unclear whether TCZ given on day 0 or admission was day 0.
    - Ferritin, CRP, D-dimer dropped. Lymphocytes up. LDH no change.
    - PaO2 and FiO2 improved by Day 7.
    - Overall mortality 11%. (all those who died got 2 doses, and died w/in 1st week after 1st TCZ dose) At day 14, 2 still vented.
    - D-dimer level at baseline was a predictor of mortality.
    - Earlier TCZ administration w/in 6d from admission assoc w/ inc likelihood of survival (HR 2.2).

- Quartuccio et al. (MedRxiv doi: https://doi.org/10.1101/2020.05.01.20078360, posted May 1)
  
  - 111 consecutive hospitalized pts, single center. 42 severe cases w/ adverse prognostic features (CRP and IL-6 up) vs 69 SOC pts.
  - severe pts all got TOCI, and 2 got anakinra after toci failure.
  - severe group : 62% ventilated, of which: 3 deaths, w/ 7/26 still on vent, 17/26 bacterial superinfection. Also 1 death on noninvasive vent, 1 serious bacterial superinfection. SOC group: no fatalities, all discharged.
  - pts in severe group were sicker and did worse. Can’t conclude anything further.

- Late April press releases for sarilumab and tocilizumab RCTs:
  
  - sarilumab, placebo controlled: April 27th announced early termination of “severe” patient enrollment, while continuation of “critical” and “multi-system organ dysfunction” patient enrollment. No effect seen w/ “severe” group or combo “severe+critical”
    - trend toward increased survival w/ higher dose.
    - trend toward vent use reduction in treatment groups vs placebo.
    - trend toward more pts off O2 and discharged in pts on higher dose.
  - tocilizumab, open-label (no placebo): French data “encouraging.”
    - primary outcomes: need for ventilation (noninvasive or mechanical) or death at day 14.
    - 129 pts: toci+SOC (incl abx) or SOC alone.
    - waiting for more information.

<table>
<thead>
<tr>
<th>anti-IL-1</th>
<th>Anakinra (IL-1R antagonist), canakinumab (IL-1beta mAb), rilonacept (IL-1 decoy receptor)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-1beta and IL-6 usually track together.</strong></td>
<td></td>
</tr>
<tr>
<td><strong>COVID rationale</strong></td>
<td>Anakinra is a gentler immunomodulator, short-acting, daily dosing. Failed in sepsis trials, but perhaps useful in subgroup w/ evidence of hyperinflammation.</td>
</tr>
<tr>
<td><strong>Data in COVID</strong></td>
<td>Anecdotal and unpublished</td>
</tr>
<tr>
<td><strong>Clinical trials</strong></td>
<td>Anakinra RCT in Italy, w/ emapalumab</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Not terribly immunosuppressive as a class esp anakinra but could mask si/sx of infection.</td>
</tr>
</tbody>
</table>

| **anti-GM-CSF** | Lenzilumab, otilimab, TJM2 (TJ003234), gimsilumab, mavrilimumab (receptor antagonist) |
| **GM-CSF activity** | Enhances activity and proliferation of neutrophils and macrophages (produce IL-6 and TNFalpha). WBC growth factor. Epithelial cell proliferation. Upstream of IL-6. Theoretically broader immunosuppressive than anti-IL-6 agents. |
| **COVID rationale** | Broadly immunosuppressive. Prevent macrophages from becoming M1 proinflammatory type. Theoretically makes sense for blocking inflammatory cytokine production. |
| **Data in COVID** | Mavrilimumab: 6 pts - see below |
| **Clinical trials** | Lenzilumab (humanigen): Phase 3 (prev studied for CMML) |
| | Otilimab: Nothing announced |
| | TJM2 (TJ003234, iMab): Phase 1b/2 |
| | Gimsilumab (Roivant): planning (just completed Phase 1) |
| | Mavrilimumab (Kiniksa): press release 6 pts. |
| **Notes** | Concern for pulmonary alveolar proteinosis esp at higher doses: not seen in RCTs for rheumatologic disease but unknown whether preexisting pulmonary inflammation changes that. |
| | Otilimab shorter acting. |

- prospective, single-arm, single center pilot, in Italy.
- 6 pts w/ severe ds, acute respiratory distress, fever, inflammatory markers.
- single dose IV. All had fever resolution and O2 req down in 1-3 days. none progressed to mechanical vent. 3/6 discharged w/in 5d.
- (cited "aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+C16+ monocyte in severe pulmonary syndrome..." GM-CSF and IFN-g up.)

<table>
<thead>
<tr>
<th>JAK inhibitors</th>
<th>Baricitinib, ruxolitinib, tofacitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK activity</td>
<td>Phosphorylate activated cytokine receptors. Generally promote inflammation.</td>
</tr>
<tr>
<td>COVID rationale</td>
<td>Inhibition of viral endocytosis by numb-associated kinase (off target effect).</td>
</tr>
</tbody>
</table>
| Clinical trials| Ruxolitinib RCT to open
Baricitinib: Next step in NIH adaptive trial, in combo w/ remdesivir.
Tofacitinib RCT in Italy |
| Notes          | Can inhibit type I interferons, concern for inhibition of viral clearance. Known increased risk of herpes zoster and HSV. Causes lymphocytopenia, neutropenia. (Favalli et al Lancet ID, Praveen et al Int J of Antimicrobial Agents, Ritchie et al. Lancet.) |

Baricitinib identified by artificial intelligence search:

<table>
<thead>
<tr>
<th>Anti-CCR5</th>
<th>Leronlimab (PRO 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5 activity</td>
<td>Pleiotropic. Directs cells to sites of inflammation.</td>
</tr>
<tr>
<td>COVID rationale</td>
<td>SARS-CoV(1) infected airway epithelial cells and macrophages express high levels of CCL5 (CCR5 ligand), could prevent pulmonary trafficking of pro-inflammatory leukocytes.</td>
</tr>
</tbody>
</table>
### Data in COVID

| Clinical trials | RCT for mild/mod disease  
|                 | RCT for severe or critical disease  
|                 | (also being studied for breast ca and tx-experienced HIV pts)  
| Notes | FDA granted eIND  

- Binds CCR5 differently than maraviroc.  
- Patterson et al. on MedRxiv doi: [https://doi.org/10.1101/2020.05.02.20084673](https://doi.org/10.1101/2020.05.02.20084673), posted May 2. (Montefiore MC)  
  - 10 critical COVID pts, got leronlimab via eIND. 6/10 hx renal transplant. High IL-6, IL-1beta, IL-8, CCL5 (RANTES), decreased CD8+Ts, SARS-CoV-2 plasma viremia. (IL-6 and CCL5 more elevated in critically ill patients vs mild/mod.)  
  - Viremia detected using “high sensitivity, digital droplet PCR” (no NP viral PCR kinetics noted)  
  - 8/10 got dialysis. (Same 8/10 got vasopressors)  
  - 4 died during 14-day study period. (medical triage possible impact)  
  - CD4/CD8 ratio normalized, IL-6 levels normalized, decrease in plasma viremia.

### Other agents

| Eculizumab, Ravlimab | Blocks C5a (terminal complement pathway) (PNH, aHUS). (See below: Diurno et al. on eculizumab) Commercially available, and can also obtain through eIND.  
| Emapalumab | Blocks IFN-gamma (approved for HLH). Trial opening to be used in combination with anakinra.  
| Syk inhibitors | Slow acting, only modest benefit in RA. Increased risk of bacterial infection.  
| Nintedanib | For pulmonary fibrosis in COVID. TKI, mostly used in solid tumor malignancy.  
| Steroids |  
| IL-17 inhibition | Ilkezumab : IL-17A mAb. RCT in China  

- Eculizumab background: Binds C5 to prevent cleavage into C5a and C5b, hence inhibiting terminal complement cascade and formation of the membrane attack complex. FDA approved for paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, myasthenia gravis. Rationale: C3 activation products detected in SARS-CoV infected mice. Increased complement activation in MERS-CoV infected mice.

  - Case series, 4 pts on noninvasive ventilation (CPAP). Dx by PCR, +CT or CXR, severe PNA (requiring O2) or ARDS, 18y+. (excluded mild/mod disease, or expected survival <24h).
  - Eculizumab x 2 doses, off label.
  - Also all on enoxaparin, lopinavir/ritonavir, HCQ, ceftriaxone, vitamin C.
  - Drop in CRP 14.6 to 3.5.
  - All recovered