Targeted Immunomodulators in COVID

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Many people contributed opinions, preprints, and time. (Stan Deresinski, Upi Singh, Will Alegria, David Ha, Shanthi Kappagoda, Beth Martin, Angela Rogers, Tamiko Katsumoto, Mark Genovese, Joe Levitt, David Miklos)

Summary: Many immunomodulator (biologics and small molecule inhibitors) have been used off-label and/or are being studied in clinical trials for COVID-19. There are a number of case series, retrospective studies, prospective studies with historical controls, and press releases on RCTs that have been released. To date, there are no randomized controlled trials demonstrating efficacy of any such agent and they are not included in the NIH COVID-19 Treatment Guidelines or in the IDSA Guidelines on Treatment and Management of Patients with COVID-19. Dexamethasone has become standard of care in COVID-19 patients requiring oxygen supplementation. The efficacy of combining dexamethasone with additional immunosuppressives is unknown, and there is reasonable concern for potential harm. We continue to recommend against the routine use of targeted immunosuppressives other than corticosteroids in COVID-19 outside the context of a clinical trial. If a biologic immunomodulator (including but not limited to anakinra and tocilizumab) is considered, please consult Infectious Diseases and Pulmonary services.

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

Evidence

Several biologic immunomodulators have been used off label and/or are being investigated in COVID-19. The basis for using these drugs have been, in part, elevated inflammatory markers and other surrogates of disease activity in severe COVID-19.

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. Sendout. 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 portend poor prognosis.
- LDH
- Possibly troponin, markers of cardiac damage

Inflammatory markers are elevated in severe COVID, and the terms “cytokine storm” and “cytokine release syndrome” have been applied liberally to this infection. “Secondary HLH” has

also been applied without histopathologic support of this term. Sinha et al. compiled cytokine level data from COVID-19 studies and prior ARDS studies, showing that cytokines in ARDS studies were orders of magnitude higher than in COVID-19. Similarly, IL-6 levels are far lower in COVID-19 than in CAR-T cell induced cytokine release syndrome (tocilizumab is indicated for the latter). Dr. Beth Martin (Hematology) has shared with us that cytokine profiles in COVID-19 also do not closely resemble classical HLH, that COVID-related coagulopathy is not typical of HLH, and she has advised against using H score or MDcalc website to evaluate for HLH in COVID-19. It remains to be understood how much inflammation is an appropriate response to viral replication versus inappropriate inflammatory cascade with subsequent tissue damage. Use of immunomodulatory biologics in sepsis and ARDS (e.g., TNF-alpha inhibition) have not demonstrated efficacy, with the exception of a possible role for anakinra in a subgroup with evidence of uncontrolled inflammation.

These agents should be avoided if there is a known bacterial or fungal infection or baseline immunosuppression. Use in pregnancy should be considered on a case-by-case basis.

anti-IL-6	Tocilizumab (IL-6R), sarilumab (IL-6R), siltuximab (IL-6)
IL-6 activity	Induction of acute phase reactants, generation of fever, tissue repair, angiogenesis, hematopoiesis. Increases CRP, fibrinogen, hepcidin. Reduces albumin synthesis. Neutrophil chemotaxis. T cell survival and differentiation. Suppresses T regs. Promotes antibody production, plasmablast survival. Known to be elevated in ARDS and predicts poor outcomes.
COVID rationale	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.
Data in COVID	Many case reports, retrospective series, prospective studies w/ historical controls, etc. Possibly an effect in patients with higher CRP?
Clinical trials	COVACTA (Roche): toci vs placebo. closed, results pending RCT toci in Italy (Roche): low enrollment. No effect. REMDACTA (Roche): remdesivir vs remdesivir/tocilizumab Sarilumab RCT (Regenon): see below. Siltuximab RCT in Spain And many more.
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. May simply mean the drug is binding its target. (IL-6 measurements not reliable after dosing).

Elevated IL-6 levels in COVID-19 patients are associated with respiratory failure and poor outcomes (Herold T et al.). There has been a great deal of interest in anti-IL-6 monoclonal

antibodies, with many reports of off-label use that are primarily case reports, case series, retrospective cohort studies, and prospective cohort studies with historical controls. Use of these agents appears to be associated with rapid resolution of fever but it is unclear whether they improve outcomes. RCTs include a number of industry sponsored studies:

1. COVACTA (Roche/Genentech): tocilizumab vs placebo. Closed. Results pending. A similar RCT was done in France, and a press release at the end of April called results "promising" but results are pending.
2. Tocilizumab RCT in Italy. Stopped early because interim analysis didn't show benefit. Enrolled 126 patients, only ⅓ of planned. Hinted at subgroup differences, results pending. Press release
3. Sarilumab RCT (Regeneron): In the US study, the moderate and severe disease arm was stopped early, with continuation of critically ill arm (in April); in the end, sarilumab did not demonstrate any benefit and those treated had more adverse events. Sarilumab press release, results pending. An RCT based on a different dosing regimen in Europe is ongoing.
4. REMDACTA (Roche/Genentech): remdesivir vs remdesivir/tocilizumab. Enrolling.
5. Siltuximab RCT in Spain ongoing.
6. Siltuximab RCT in US: planned

Some earlier data that led to the RCTs included Xu et al. PNAS, Gritti et al. MedRxiv, Luo et al. J Med Virol, Sciascia et al. Clin Exp Rheum, Quartuccio et al. MedRxiv. Xu et al. was a description of 21 patients treated with tocilizumab without a control group, in which 19 were discharged from hospital. Gritti et al. was a retrospective, uncontrolled description of 21 pts treated with siltuximab, in which 33% improved, 43% stable, and 24% worsened, with plan to publish a case-control study with longer follow up. Luo et al. was a retrospective, uncontrolled description of 15 pts, half on methylprednisolone, with mixed results. Sciascia et al was prospective, uncontrolled on tocilizumab; D-dimer was a predictor of mortality, and earlier tocilizumab administration was associated with survival. Quartuccio et al. similar. There have been many other preprints and publications with similar designs.

Three interesting non-RCT tocilizumab studies:

1. Martinez-Sanz et al. MedRxiv: 1229 pts from 17 hospitals in Spain, nonrandomized. Comparisons: toci vs untreated, and toci-high CRP vs toci-normal CRP (baseline CRP). In unadjusted analysis, mortality was higher in the toci group (HR 1.53). Interestingly, among pts w/ baseline CRP >150 mg/L, toci was associated with a decreased risk of death (aHR 0.34) and ICU-or-death (aHR 0.38); this association was not observed among those with baseline CRP <150. Thus, patient selection may be important to see an effect.
2. Sanz Herrero et al. J Int Med: Tocilizumab vs tocilizumab+methylprednisolone. Tocilizumab given to >70 pts, and methylpred was added to their SOC 3/27, so control group is essentially historical. Mortality significantly lower in group that got methylprednisolone (20% vs 63%). Notable for combination of immunosuppressives, and comparison (historical) with steroid effect.
3. Quartuccio et al. J Med Virol: appears to be a subgroup analysis of the above study. 24 pts all treated with tocilizumab. No baseline differences between survivors and nonsurvivors, including IL-6 level at baseline (prior to tocilizumab). IL-6 levels *after* tocilizumab dose significantly higher in nonsurvivors than in survivors. 28% survivors and 50% nonsurvivors had gotten steroids.
4. Somers et al. MedRxiv: 154 pts (78 toci vs 76 comparator). Like many of the prior published studies, also retrospective, observational. Control pts were older, had more

lung disease, got less steroids, had higher D-dimer, and were more likely to have been OSH transfers and transferred to mechanical vent. With IPTW adjustment, pts treated w/ tocilizumab had lower mortality and higher rates of superinfection, but w/ adjustment they argue no difference in mortality among those w/ superinfection.

anti-IL-1	Anakinra (IL-1R antagonist), canakinumab (IL-1beta mAb), rilonacept (IL-1 decoy receptor)
IL-1 alpha and beta activity	Alarmin in cell necrosis. Fever induction, pain sensitization, bone and cartilage destruction, production of acute phase reactants. MyD88 and NFkB phosphorylation → transcription of proinflammatory genes. Downsteam of inflammasome assembly. IL-1beta and IL-6 usually track together.
COVID rationale	Anakinra is a gentler immunomodulator, short-acting, daily dosing. Failed in sepsis trials, but perhaps useful in subgroup w/ evidence of hyperinflammation.
Data in COVID	Case series and a retrospective cohort study
Clinical trials	Anakinra alone or in combination with other immunosuppressives, including emapalumab, ruxolitinib, tocilizumab, baricitnib
Notes	Not terribly immunosuppressive as a class esp anakinra but could mask si/sx of infection.

No RCT data has been published or made available through press release at this time. There have been a number of case reports, not listed here. Small studies have based patient selection on elevated inflammatory markers.

1. In a retrospective cohort study with historical controls, Cavalli et al. Lancet Rheumatology treated 35 pts with respiratory failure, pneumonia, and elevated inflammatory markers (CRP≥100 mg/L and/or ferritin ≥900 ng/ml) on CPAP with anakinra (two different doses). None got steroids, all got HCQ and LPV/r. Low dose stopped as it was ineffective. Comparing high dose anakinra (n=29) vs historical controls (n=16): No difference in proportion discharged to normal activity (44 vs 45%). Of those still hospitalized, control pts more likely to have died (44% vs 10%), while anakinra pts more likely to still be in hospital on vent/O2 (34%) including half on mechanical ventilation (17%). One possible interpretation is that those who would improve in 21 days will do so with or without anakinra, while 21 days is too short to know whether there is a difference in sustained survival.
2. Navarro-Milan et al. Arthritis Rheum also selected pts with respiratory failure by elevated inflammatory markers (ferritin > 1000 ng/ml + fever + one other marker of inflammation) for this retrospective case series. Comparison was drawn between early vs late initiation of anakinra. 14 met criteria. 11 received high dose anakinra, while 3 did not. All 3 who did not get anakinra required mechanical ventilation. Of the 11 who received anakinra: 7 pts started anakinra ≤36h after onset of respiratory failure (early initiation), and 4 started it ≥4d in (late initiation). All 7 early initiation pts remained off mechanical ventilation and

were discharged. All 4 late initiation pts required mechanical ventilation; 3 were extubated (1 still hospitalized), 1 died. 4 in each group (early and late) got methylpred.
3. Pontali et al. J Allergy Clin Immunol described 5 pts with baseline elevated inflammatory markers who received IV anakinra. All did well and were discharged.
4. Day et al. Br J Haematol described three pts with acute leukemia and COVID in whom anakinra was used without complications.

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: prospective study w/ contemporaneous controls, not randomized Compassionate use lenzilumab
Clinical trials	Lenzilumab (humanigen): Phase 3 (prev studied for CMML) Otilimab: planning TJM2 (TJ003234, iMab): Phase 1b/2 Gimsilumab (Roivant): BREATHE- enrolling (just completed Phase 1) Mavrilimumab (Kiniksa): enrolling
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.

No RCT data yet. None of these drugs have FDA approved indications.

1. De Luca et al. Lancet Rheumatology: mavrilimumab prospective cohort study with contemporaneous controls (but not randomized: no drug available, shortage or drug, or refused consent). Pts w/ respiratory failure not on mechanical ventilation, with elevated inflammatory markers (LDH increased AND either CRP >100 mg/L or ferritin >900 ug/L). 13 pts received mavrilimumab, and 26 controls got SOC. At day 28, all mavrilimumab pts and 65% control pts had improved, w/ earlier improvement (8d vs 19d) and earlier discharge (10d vs 20d) seen in mavrilimumab pts. 8% mavrilimumab vs 35% control on mechanical vent or died, and 0% tx vs 27% controls died (neither measure achieved statistical significance).
2. Temesgen Z et al. MedRxiv: Lenzilumab compassionate use IND at Mayo Clinic, no controls. 12 pts, did not use inflammatory markers for inclusion; excluded systemic infection. No pre-specified study endpoints. Clinical improvement in 11 out of 12. Median time to discharge 5 days. Improvement in CRP and IL-6 on day 3. All had at least one comorbidity (DM, HTN, obesity, CKD, CAD, renal transplant, lung disease, OSA, COPD, RAD). All had elevation in at least one inflammatory marker at baseline (ferritin, IL-6, CRP, D-dimer). No difference in mean PMNs or Hgb.

JAK inhibitors	Baricitinib, ruxolitinib, tofacitinib
JAK activity	Phosphorylate activated cytokine receptors. Generally promote inflammation.
Data in COVID	Cohort studies, one RCT in China (Cao et al.). Combination with eculizumab (Giudice et al.)
COVID rationale	Inhibition of viral endocytosis by numb-associated kinase (off target effect), or by AP-2 associated protein kinase 1 (AAK1). SARS-CoV2 enters cells through receptor-mediated endocytosis. AAK1 is a regular of receptor-mediated endocytosis. Baricitinib has high affinity for AAK1. (Sorrell F, Szklarz M, et al. Family-wide structural analysis of human numb-associated protein kinases. Structure 2016; 24:401-11.)
Clinical trials	ACTT-II (NIH): baricitinib/remdesivir vs remdesivir (closed) Ruxolitinib RCT (Incyte) Tofacitinib RCT Many studies registered.
Notes	Can inhibit production of 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.)

Many RCTs planned and enrolling. ACTT-II (NIH) compared remdesivir vs baricitinib/remdesivir, results pending. One RCT with these agents has been published thus far: Cao et al. J Allergy Clin Immunol, ruxolitinib vs placebo, randomized, single-blind, China. (No remdesivir) Severe COVID not on vent. Multiple comorbidity exclusions. Did not achieve enrollment target. 70% in each group on steroids. No significant difference in % achieving clinical improvement. Median time to clinical improvement: ruxo 12d vs control 15d (not significant). 0 ruxo and 3 control patients were intubated, 0 vs 3 required pressors, 0 vs 2 required renal replacement, and 0 vs 3 died. No difference in viral clearance (ruxo 13d, control 12d). Possibly underpowered, perhaps any differences were diminished by steroid use in 70% of each group.

Of non-RCT data, there have been a number of case reports and there have been several small to larger studies published:

1. Cantini et al. J Infection: Baricitinib. (Italy) 12 consecutive hospitalized patients 3/16-3/30 w/ moderate COVID, and 12 historical controls (last consecutive pts admitted before 3/16). Inflammatory markers not used for inclusion. Baricitinib tx vs control: ICU transfer 0 vs 33%, discharge by week 2 in 58% vs 85%, and decreased O2 requirement.
2. La Rosee et al, Leukemia: Ruxolitinib in pts w/ high inflammation scores ("CIS" = COVID-19 Inflammation Score). Prospective, single-arm, no controls, Germany. Out of 105 pts w/ COVID (3/30-4/15), only 14 had CIS ≥10 out of 16 points, and thus n = 14 receiving ruxo. 12/14 achieved significant reduction of CIS, with sustained clinical improvement in 11/14.

3. Giudice et al. Frontiers Pharmacol: Combination ruxolitinib+eculizumab vs SOC. 17 consecutive cases of COVID ARDS tx ruxolitinib+eculizumab (n = 7) vs SOC controls (n = 10). Not randomized; unclear how it was decided who was treated. *Steroids were administered in 5/7 ruxo/ecu pts and 3/10 controls.* Ruxo/ecu treated pts had significant improvements in respiratory sx and radiographic findings vs controls. 1 pt died in each group. Mechanical ventilation in 1 pt in control group, 0 in tx group (but the 1 pt who died in the tx group died of ARDS).
4. Titanji et al. Clin Inf Dis: Barcinitib+HCQ. Emory. 15 pts w/ moderate to severe COVID-19 (at least one of: hospitalized, rising inflammatory markers, pneumonia+O2 requirement). Retrospective, no controls. 12 recovered (off O2 in hospital or discharge +/- O2); 11 seemed to improve after baricitinib given. 3 died. 2 developed bacterial or fungal infection.

BTK inhibitor	Ibrutinib, acalabrutinib
BTK activity	Mediator of B cell receptor signaling, required for B cell development TLR-mediated recognition of pathogens, Fc receptor signaling. Dendritic cell and macrophage maturation and recruitment. Regulator of NLRP3 inflammasome.
COVID rationale	Dampening TLR-mediated inflammation, macrophage signaling and activation
Data in COVID	Case reports, case series
Clinical trials	RCTs ibrutinib (Abbvie) and acalabrutinib (AstraZeneca) planned and/or enrolling. Ibrutinib RCT enrolling at Stanford
Notes	BTK is involved in adaptive and innate immunity. Role of BTK in innate immunity has been underscored by risk of invasive aspergillosis with ibrutinib.

Acalabrutinib was used off label by Roschewski et al. Science Immunology in 19 pts with severe COVID (11 on supplemental O2, 8 on mechanical ventilation). No comparison group. 18/19 had increasing O2 requirements at baseline. After treatment, most patients had reduced O2 requirement and improvement in CRP, IL-6, and ALC. At the end of treatment, 8/11 out of 11 pts initially on supplemental O2 were discharged without O2, and 4/8 pts initially on mechanical ventilation were extubated.

Stanford is enrolling patients in an industry sponsored ibrutinib RCT at this time.

Anti-CCR5	Leronlimab (PRO 140)
CCR5 activity	Pleiotropic. Directs cells to sites of inflammation.

COVID rationale	SARS-CoV(1) infected airway epithelial cells and macrophages express high levels of CCL5 (CCR5 ligand), could prevent pulmonary trafficking of pro-inflammatory leukocytes.
Data in COVID	Patterson et al.
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.

Leronlimab RCTs are recruiting-- no results in press releases or preprints yet. Compassionate use in 10 pts was described in Patterson et al. MedRxiv (Montefiore). 6/10 had hx of renal transplant. 8/10 received renal replacement and vasopressors. 4 died during the 14-day study prior. CD4/CD8 ratio normalized, IL-6 levels normalized, decrease in plasma viremia.

Other agents	
Eculizumab, Ravulizumab	Blocks C5a (terminal complement pathway) (PNH, aHUS). (See below: Diurno et al. on eculizumab) Commercially available, and can also obtain through eIND. Alexion planning for RCT of ravulizumab in severe COVID.
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.
IL-17 inhibition	Ixekizumab : IL-17A mAb. RCT in China Ustekinumab : case report of pt w/ psoriatic arthritis on ustekinumab who had mild case of COVID.

Minimal data on these agents in COVID thus far. RCTs are being planned or are recruiting for scores of other immunomoduators. Of the C5a inhibitors, available data in COVID includes:

1. Giudice et al. Frontiers Pharmacol: see above (ruxolitinib/eculizumab vs SOC)
2. Diurno et al. Eur Rev Med Pharmacol Sci: Case series of 4 pts on CPAP for severe COVID. All recovered.