Supplemental Text 1: IL-6 in COVID-19 Infection

The review by Leisman et al (2020) demonstrated IL-6 concentrations in other conditions associated with markedly elevated cytokine levels (i.e., sepsis, CAR-T-associated cytokine release syndrome, and non-COVID-19 ARDS) were anywhere from 12 to 100 times higher than the IL-6 concentrations associated with severe or critical COVID-19 infection. The authors suggest that cytokine storm may not play as pivotal a role in COVID-19-induced end-organ dysfunction as previously thought. However, it is important to consider that these other hyperinflammatory conditions analyzed in the aforementioned have differing pathophysiology and biology compared to COVID-19, and as such a head-to-head comparison of IL-6 levels may not be entirely appropriate in evaluating the role of the cytokine response in COVID-19. In fact, studies have shown that elevated IL-6 levels in COVID-19 are associated with higher SARS-CoV-2 viral load and poorer prognosis, thus supporting the central role of a heightened inflammatory response in COIVD-19 (1,2). This observation does not preclude the possibility that other cytokines associated with the release syndrome (e.g., IL-1β, which is more directly regulated by colchicine than IL6)) may be equally or more important than IL-6 in COVID-19 responses.

Since the start of the COVID-19 pandemic, significant resources have been allocated to investigate the therapeutic efficacy of anti-IL-6 therapies with respect to severe COVID-19 infection. Thus far, the results of these studies have been equivocal at best. In a meta-analysis by Lan et al, although patients treated with tocilizumab were found to have lower all-cause mortality compared to the placebo group, the results did not achieve statistical significance, with risk of ICU admission and the need for mechanical ventilation similar between the two groups (3). None of the included studies were randomized controlled trials, however, and in many of them baseline characteristics/illness severity of patients were not matched. Larger-scale randomized trials have shown similar results, with trials of both tocilizumab and sarilumab failing to meet their primary endpoint (4,5). Furthermore, some studies have demonstrated that the immunosuppressive effects of anti-IL-6 therapies may actually contribute to adverse effects in COVID-19 patients due to secondary bacterial or, less commonly, fungal infections (3,6). Despite these overall

disappointing results, ongoing studies continue to investigate anti-IL-6 agents with respect to combination therapies, and alternative dosing regimens that may hold promise for COVID-19 infection.

Although colchicine has been shown to inhibit IL-6 secretion, it has multiple additional mechanisms of action that may potentially temper the COVID-19-induced hyperinflammatory response. Additionally, colchicine is not immunosuppressive compared to its anti-IL-6 counterparts, and thus may be a more suitable COVID-19 treatment. Finally, most studies of colchicine have aimed to dampen inflammation at an early stage, whereas most studies of anti-IL-6 therapeutics have been directed at treating the COVID-19 inflammatory response at a very advance stage of the infection, when targeting a single cytokine may simply be too little, too late.

References

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Supplemental Table 1. Studies Reporting the Risk of Pneumonia with Colchicine

Study	Design	Result
Nidorf et al, NEJM 2020	Prospective double-blind trial, colchicine vs placebo	No increase in pneumonia in colchicine group
Tardif et al, NEJM 2020	Prospective double-blind trial, colchicine vs placebo	Increased pneumonia in colchicine group
Besisow et al, European Journal of Cardio-Thoracic Surgery 2018	Prospective randomized study, colchicine vs placebo	One patient with pneumonitis in colchicine group vs none in placebo group
Tsai et al, Frontiers in Pharmacology 2019	Retrospective cohort study, colchicine vs no colchicine	Higher cumulative incidence of pneumonia in colchicine group; higher with longer exposure
Spaetgens et al, Scientific Reports 2017	Retrospective cohort study, colchicine vs no colchicine	Increased pneumonia among past but not current colchicine users

Supplemental Table 2. Published and Ongoing Studies of Colchicine in COVID-19

eGFR – estimated glomerular filtration rate, **QTc** – corrected QT interval, **CRP** – c-reactive protein, **LDH** – lactate dehydrogenase, **IL-6** – interleukin-6, **SARS** – severe acute respiratory syndrome, **CK** – creatinine kinase, **CrCL** – creatinine clearance, **TNF-alpha** – tumor necrosis factor-alpha, **GDF-15** – growth differentiation factor-15, **BNP** – B-type natriuretic peptide, **IBD** – inflammatory bowel disease,
* Patients with hypersensitivity to colchicine, <18, and pregnant were not included in most studies

Study (Date)	Clinical Setting	Design (n)	Exclusion Criteria*	Intervention	Primary Outcome(s)	Secondary Outcome(s)	Significant Results	Inflammatory Measures	Reference
GRECCO-19 (April 3 to April 27, 2020)	Early Inpatient	Randomized, open-label vs usual care (105)	Hepatic failure, eGFR <20 mL/min/1.73 m^2, QTc ≥ 450 ms, early mechanical ventilation	Colchicine 1.5mg loading dose + 0.5mg after 60 minutes, then 0.5mg BID	1) maximum high-sensitivity cardiac troponin level, 2) time for CRP to reach >3x ULN, 3) Clinical deterioration by WHO scale	1) % requiring mechanical ventilation, 2) all-cause mortality, 3) adverse events	Clinical primary end point lower (p=0.02), Maximum D-dimer lower (p=0.04), Higher diarrhea incidence (p=0.003)	CPK, CRP, d-dimer, ferritin, LDH, procalcitonin, troponin	Deftereos SG, Giannopoulos G, Vrachatis DA, et al. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. JAMA Netw Open. 2020;3(6):e2013136.
Scarsi et al. (March 5 to April 5, 2020)	Early Inpatient	Randomized, open-label vs usual care (262)	Renal failure	Colchicine 1mg per day (reduced to 0.5mg if severe diarrhea)	Survival rates	Clinical and laboratory comparison	Higher survival (84% vs 64%, p<0.001)	CRP, Ferritin	Scarsi M, Piantoni S, Colombo E, et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalised patients with COVID-19 pneumonia and acute respiratory distress syndrome. Ann Rheum Dis. 2020.
Lopes et al. (April 11 to July 6, 2020)	Inpatient, moderate to severe disease	Randomized, double-blind, placebo-controlled (38)	Weight ≤ 50 kg, abnormal calcium or potassium levels, QTc ≥ 450 ms, diarrhea causing dehydration, porphyria, myasthenia gravis, uncontrolled arrhythmia, metastatic cancer, immunosuppressive chemotherapy, CYP3A4 inhibitor use, hepatic failure	Colchicine 0.5mg TID for 5 days, then 0.5mg BID for 5 days	1) Supplemental oxygen, 2) LOS, 3) ICU admission, 4) ICU LOS, 5) all-cause mortality	1) CRP, 2) LDH and WBC relation, 3) adverse events, 4) QT interval >450 ms.	Less need for supplemental oxygen (p=0.01), Shorter LOS (p=0.01), Reduction in CRP (p<0.001)	CRP, LDH	Lopes MIF, Bonjorno LP, Giannini MC, et al. Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial. medRxiv. [Preprint]. Date Accessed: August 25, 2020. https://doi.org/10.1101/2020.08.06.20169573.

Dalili et al. (March 20, 2020 to *present)*	Early Inpatient	Randomized, double-blind, placebo-controlled (80, anticipated)	Hypoxia, hepatic failure, eGFR < 20 mL/min/1.73 m^2	Colchicine 1.5mg loading dose, then 0.5mg BID	1) CRP change, 2) Clinical deterioration by WHO scale, 3) PCR viral load change, 4) CT severity	LDH change	Ongoing	CRP, LDH	ClinicalTrials.gov [Internet]. Tehran, Iran: National Library of Medicine (US). 2020 April 24. Identifier NCT04360980. The Effects of Standard Protocol With or Without Colchicine in Covid-19 Infection; 2020 March 20 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04360980.
Mostafaie et al. (April 1, 2020 to *present)*	Inpatient	Randomized, double-blind, placebo-controlled (200, anticipated)	Severe kidney dysfunction	Colchicine plus Phenolic Monoterpene Fractions	All-cause mortality	1) Change in clinical manigestation, 2) LOS, 3) Lab parameters (CRP, Lymphocytes, LDH, IL-6, ESR)	Ongoing	CRP, ESR IL-6, LDH	ClinicalTrials.gov [Internet]. Kermanshah, Iran: National Library of Medicine (US). 2020 May 18. Identifier NCT04392141. Colchicine Plus Phenolic Monoterpenes to Treat COVID-19; 2020 April 1 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04392141.
COLCOVID (April 17, 2020 to *present)*	Early or Late Inpatient	Randomized, open-label vs usual care (2500, anticipated)	No evidence of SARS	Colchicine 1.5mg loading dose, then 0.5mg 2 hours later, then 0.5mg BID for 14 days or until discharge	All-cause mortality	Composite outcome: mechanical ventilation or death	Ongoing	None	ClinicalTrials.gov [Internet]. Santa Fe, Argentina: National Library of Medicine (US). 2020 March 31. Identifier NCT04328480. The ECLA PHRI COLCOVID Trial. Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients. (COLCOVID); 2020 April 17 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04328480.
COLVID-19 (April 18, 2020 to *present)*	Early Inpatient	Randomized, open-label vs usual care (308, anticipated)	Severe diarrhea, CrCL < 30 mL/min, liver damage, CYP3A4 inhibitor use, tocilizumab use, neutrophilia, thrombocytopenia, diverticulitis or bowel perforation, ICU admission	Colchicine 0.5mg TID for 30 days	Rate of entering critical stage	1) WBC trend, 2) SOFA change, 3) Lab recovery (CK, ALT, ferritin), Disease remission, 4) Adverse events	Ongoing	CK, ferritin	ClinicalTrials.gov [Internet]. Milan, Italy: National Library of Medicine (US). 2020 May 5. Identifier NCT04375202. Colchicine in COVID-19: a Pilot Study (COLVID-19); 2020 April 18 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04375202.
ColCOVID-19 (April 20, 2020 to *present)*	Inpatient	Randomized, open-label vs usual care (310, anticipated)	Hypoxia, unstable, hepatic failure, antiviral use	Colchicine 1mg daily	1) Clinical improvement by WHO, 2) Discharge	1) Death, 2) Clinical change by WHO, 3) Mechanical ventilation, 4) LOS, 5) Time to mortality, 6) Time to PCR negative, 7) Fever remission time	Ongoing	None	ClinicalTrials.gov [Internet]. Parma, Italy: National Library of Medicine (US). 2020 March 26. Identifier NCT04322565. Colchicine Counteracting Inflammation in COVID-19 Pneumonia (ColCOVID-19); 2020 April 20 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04322565.

ACTCOVID19 (April 21, 2020 to *present)*	Early Outpatient and Early Inpatient	Randomized, open-label colchicine vs IFN-beta vs ASA vs rivaroxaban vs usual care (4000, anticipated)	Advanced kidney disease, advanced liver disease, CYP3A4 inhibitor use, therapeutic anticoagulation or antiplatelet use	Outpatient: Colchicine 0.6mg BID for 3 days, then 0.6mg daily for 25 days. Inpatient: 1.2mg loading dose, then 0.6mg 2 hours later, then 0.6mg BID for 28 days	Outpatient: Composite hospitalization or death; Inpatient: Composite: mechanical ventilation or death	1) Clinical deterioration by WHO, 2) Composite: MACE	Ongoing	None	ClinicalTrials.gov [Internet]. Ontario, Canada: National Library of Medicine (US). 2020 March 27. Identifier NCT04324463. Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACTCOVID19); 2020 April 21 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04324463.
COMBATCOVID19 (April 26 to June 14, 2020)	Inpatient	Randomized, open-label vs usual care (70, anticipated)	Hypoxia using >8L supplemental oxygen, unstable, cirrhosis, liver injury, CrCL < 30 mL/min, early mechanical ventilation, CYP3A4 inhibitor use, chemotherapy use	Colchicine 1.2mg loading dose, then 0.6mg 2 hours later, then 0.6mg BID for 14 days or until discharge	% requiring supplemental oxygen >8L NC	1) Mechanical ventilation, 2) LOS, 3) Mortality, 4) Maximum CRP, 5) Maximum troponin	Pending Publication	CRP, troponin	ClinicalTrials.gov [Internet]. Brooklyn, New York: National Library of Medicine (US). 2020 April 27. Identifier NCT04363437. COlchicine in Moderate-severe Hospitalized Patients Before ARDS to Treat COVID-19 (COMBATCOVID19); 2020 April 26 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04363437.
COL-COVID (April 30, 2020 to *present)*	Early Inpatient	Randomized, open-label vs usual care (102, anticipated)	Early mechanical ventilation, IBD, previous neuromuscular disease, < 1 year prognosis due to other disease, eGFR <30 mL/min, cirrhosis, liver injury, immunosuppressive or immunomodulatory use within 6 months	Colchicine 1mg, then 0.5mg 2 hours later, then 0.5mg BID for 7 das, then 0.5mg daily for 28 days total	1) Clinical deterioration by WHO, 2) IL-6 changes	1) Clinical improvement by WHO scale, 2) SOFA change, 3) NEWS change, 4) Mechanical ventilation time, 5) Supplemental oxygen, 6) Lab changes (CRP, TNF, GDF-15, IL-1β, D-dimer, Leukocytes, Lymphocytes, Platelets, LDH, Ferritin, Troponin, BNP, PCR status), 7) LOS, 8) ICU days, 9) Mortality	Ongoing	BNP, CRP, d-dimer, GDF-15, IL-1β, IL-6, LDH, TNF-alpha, troponin	ClinicalTrials.gov [Internet]. Murcia, Spain: National Library of Medicine (US). 2020 April 17. Identifier NCT04350320. Trial to Study the Benefit of Colchicine in Patients With COVID-19 (COL-COVID); 2020 April 30 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04350320.

COLHEART-19 (May 1, 2020 to *present)*	Inpatient	Randomized, open-label vs usual care 150 (anticipated)	No cardiac injury, CYP3A4 inhibitor use, severe hematologic disorder, severe neuromuscular disorder, severe renal impairment with hepatic impairment	Colchicine 0.6mg BID for 30 days	Composite of all-cause mortality, mechanical ventilation, or mechanical circulatory support	1) Lab changes (Troponin, BNP, CRP, D-dimer), 2) LVEF change, 3) Time to primary endpoint, 4) Number of mechanical ventilation and circulatory support, 5) Rehospitalization, 6) All-cause mortality	Ongoing	BNP, CRP, d-dimer, troponin	ClinicalTrials.gov [Internet]. Los Angeles, California: National Library of Medicine (US). 2020 April 21. Identifier NCT04355143. Colchicine to Reduce Cardiac Injury in COVID-19 (COLHEART-19); 2020 May 1 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04355143.
COLORIT (May 8 to August 23, 2020)	Unspecified	Randomized, open-label 3:1:1:3 (colchicine, ruxolitinib, secukinumab, control) (70, anticipated)	No hypoxia, normal CRP, liver failure, GFR < 20 mL/min, QTc > 450 ms, steroid or immunosuppressive use, active cancer, early mechanical ventilation	Colchicine 0.5mg BID for 3 days, then 0.5mg daily/BID based on weight for 7 days	Change from baseline in CAS COVID 19	1) Combination time to death or mechanical ventilation, 2) Lab changes (CRP, D-dimer), 3) EQ-5D change, 4) Lung CT exposure area change	Pending Publication	CRP, d-dimer	ClinicalTrials.gov [Internet]. Moscow, Russia: National Library of Medicine (US). 2020 May 27. Identifier NCT04403243. COLchicine Versus Ruxolitinib and Secukinumab In Open Prospective Randomized Trial (COLORIT); 2020 May 8 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04403243.
ColchiVID (May 27, 2020 to *present)*	Inpatient	Randomized, double-blind, placebo-controlled (174, anticipated)	> 70 years old, CrCL < 30 mL/min, liver failure, CYP3A4 inhibitor use	Colchicine 1.5mg loading dose, then 0.5mg BID for 10 days	1) Number of patients with improvement in body temperature, myalgia, arthralgia, total lymphocyte count, D-dimer, fibrinogen, and ferritin, 2) Progression to severe disease	None	Ongoing	d-dimer, ferritin, fibrinogen	ClinicalTrials.gov [Internet]. Mexico City, Mexico: National Library of Medicine (US). 2020 April 29. Identifier NCT04367168. Colchicine Twice Daily During 10 Days as an Option for the Treatment of Symptoms Induced by Inflammation in Patients With Mild and Severe Coronavirus Disease (ColchiVID); 2020 May 27 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04367168.
COLCOVIDBD (July 4, 2020 to *present)*	Early Inpatient	Randomized, double-blind, placebo-controlled (300, anticipated)	Hepatic failure, eGFR <30 mL/min, decompensated heart failure, QTc > 450 ms, IBD, chemotherapy use	Colchicine 1.2mg BID for 1 day, then 0.6mg daily for 13 days	Time to deterioration by 2 points on 7-grade clinical status scale.	1) LOS, 2) Supplemental oxygen, 3) Mechanical ventilation, 4) Mortality	Ongoing	None	ClinicalTrials.gov [Internet]. Dhaka, Bangladesh: National Library of Medicine (US). 2020 August 26. Identifier NCT04527562. Colchicine in Moderate Symptomatic COVID-19 Patients: Double Blind, Randomized, Placebo Controlled Trial to Observe the Efficacy (COLCOVIDBD); 2020 July 4 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04527562.

Della-Torre et al. (Published May 31, 2020)	Outpatient	Non-randomized, open label case series (9)	None	Colchicine 1mg BID for 1 day, then 1mg daily until afebrile for 3 days	One patient hospitalized for 4 days	2 patients with mild diarrhea		None	Della-Torre E, Della-Torre F, Kusanovic M, et al. Treating COVID-19 with colchicine in community healthcare setting. Clin Immunol. 2020;217:108490.
COLCORONA (March 23, 2020 to *present)*	Early Outpatient	Randomized, double-blind, placebo-controlled (6000, anticipated)	≤ 40 years old, no high-risk criteria, unstable, IBD, neuromuscular disease, eGFR <30 mL/min, cirrhosis, liver injury, chemotherapy use	Colchicine 0.5mg BID for 3 days, then 0.5mg daily for 27 days	Composite: Hospitalization or Death	1) All-cause mortality, 2) Hospitalization, 3) Ventilation	Ongoing	None	ClinicalTrials.gov [Internet]. Montreal, Canada (Global sites): National Library of Medicine (US). 2020 March 26. Identifier NCT04322682. Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA) (COVID-19); 2020 March 23 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04322682.
ACTCOVID19 (April 21, 2020 to *present)*	Early Outpatient and Early Inpatient	Randomized, open-label colchicine vs IFN-beta vs ASA vs rivaroxaban vs usual care (4000, anticipated)	No high-risk criteria, advanced kidney disease, advanced liver disease, CYP3A4 inhibitor use, therapeutic anticoagulation or antiplatelets	Outpatient: Colchicine 0.6mg BID for 3 days, then 0.6mg daily for 25 days. Inpatient: 1.2mg loading dose, then 0.6mg 2 hours later, then 0.6mg BID for 28 days	Outpatient: Composite hospitalization or death; Inpatient: Composite: mechanical ventilation or death	1) Clinical deterioration by WHO, 2) Composite: MACE	Ongoing	None	ClinicalTrials.gov [Internet]. Ontario, Canada: National Library of Medicine (US). 2020 March 27. Identifier NCT04324463. Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACTCOVID19); 2020 April 21 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04324463.
COLCHI-COVID (May 25, 2020 to *present)*	Early Outpatient	Randomized, open-label vs usual care (1028, anticipated)	≥ 70 years old, no high-risk criteria, severe gastrointestinal disease, neuromuscular disease, eGFR <30 mL/min, cirrhosis, liver injury, chemotherapy use, CYP3A4 inhibitor use,	Colchicine 0.5mg BID for 3 days, then 0.5mg daily for 18 days	1) Mortality, 2) Hospitalization	None	Ongoing	None	ClinicalTrials.gov [Internet]. Cantabria, Spain: National Library of Medicine (US). 2020 June 4. Identifier NCT04416334. PREEMPTIVE THERAPY WITH COLCHICINE IN PATIENTS OLDER THAN 70 YEARS WITH HIGH RISK OF SEVERE PNEUMONIAE DUE TO CORONAVIRUS (COLCHI-COVID); 2020 May 25 [cited 2020 August 26]. Available from: https://clinicaltrials.gov/ct2/show/NCT04416334.