Northwestern Medicine ASP Evidence Review for Inpatient Treatment Options for COVID-19

The listed agents represent potential treatments for inpatient cases of COVID-19 largely based on limited evidence, none proven effective to date.
Careful clinical consideration should be applied when deciding to use the agents listed in this select evidence review.
This document should not be used as empiric or definitive treatment guidelines.
Evidence is continuing to evolve, as such this document will be updated accordingly.

AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Remdesivir (GS-5734)				
Antiviral with activity against Ebola, MERS, SARS *Prodrug nucleotide analog of adenosine triphosphate; incorporates into nascent viral RNA chains and results in premature termination.* Gilead	**Dose**: 200mg IV x1 on day 1 then 100mg IV daily for the duration of the hospital course up to 10 days total **Duration**: • EUA: 5 days for most patients • Immunocompromised patients on mechanical ventilation or chronic vent pts receiving EUA: may extend to 10 days • Clinical trial: 5 or 10 days (determined by PI)	**NMH updated EUA remdesivir criteria (as of 10/5):** 1. Hospitalized patients with suspected or confirmed COVID-19 a. Hypoxemic with SpO2<94% on room air or requiring supplemental oxygen b. ALT < 5x ULN c. Immunosuppression* 2. ID consult recommended for remdesivir use in suspected COVID-19 despite negative PCR *Immunosuppression defined as pts with any of the following: i. ≥20 mg/day prednisone (or equivalent) for at least 2 weeks ii. Organ transplant receiving immunosuppressive medications iii. Cancer patients on chemotherapy or those with hematological malignancies **- Investigational (NMH) via ACTT-III**	**FDA EUA Fact Sheet for Providers** **FDA EUA Fact Sheet for Patients** **FDA MedWatch Adverse Event Reporting for patients receiving EUA remdesivir**	**AE:** Abnormal LFTs, hepatotoxicity, abnormal INR, PT & PTT, reversible kidney injury, nausea, vomiting, diarrhea, headache, rash **Contraindications/Precautions:** Monitor for hepatotoxicity, monitor for nephrotoxicity as IV formulation contains cyclodextrin Should not be co-administered with HCQ or CQ due to antagonistic effects

NMH is enrolled as study site for remdesivir use in Adaptive COVID-19 clinical trial (ACTT-III) (remdesivir + interferon beta-1a vs. remdesivir + placebo)

Evidence

- ACTT-2 trial Press Release: Initial data from randomized, double-blind, controlled trial of > 1000 patients to evaluate the efficacy and safety of baricitinib 4mg + remdesivir vs remdesivir alone in hospitalized COVID-19 patient. The combination (B + R) led to a statistically significant reduction in median recovery time by approximately one day. (Press Release)
- Comparative analysis of remdesivir versus a historical cohort receiving standard of care in adults with severe COVID. A total of 312 patients from the phase III SIMPLE randomized, open-label trial of remdesivir were compared with 818 patients from a real-world, retrospective cohort sample of patients receiving standard of care (non-remdesivir cohort). Study included hospitalized patients with confirmed SARS-CoV-2, O2 sat <94% or requiring supplemental oxygen, and had pulmonary infiltrates. Multivariable logistic regression was used to estimate the effect of remdesivir. Findings suggest improved clinical recovery of remdesivir treated patients (74.4% vs 59.0%) by day 14, and 62% reduction in mortality (OR 0.38; 7.6% vs 12.5%; P=0.001). The comparative design of this study draws skepticism and results should be interpreted with caution. (Olender)
- Preliminary results from double-blind RCT comparing remdesivir (n=538) versus placebo (n=521) in hospitalized patients with COVID-19 and at least one of the following criteria: infiltrates on chest imaging, SpO2 ≤94% on room air, or supplemental oxygen requirement including mechanical ventilation. Pts were excluded if eGFR < 30ml/min, LFTs > 5x ULN, pregnant, or breastfeeding. Among 1063 patients, those treated with remdesivir had a shortened median time to recovery (11d v 15d) compared with placebo. Significant clinical status improvement, measured by 8-point ordinal scale, was seen with remdesivir compared to placebo (59.2% v 49.5%, OR 1.5). No significant difference was found for mortality at 14 days although it was numerically lower with remdesivir (7.1% v 11.9%). Serious adverse events were experienced in 21.1% of patients receiving remdesivir compared to 27.0% in those receiving placebo. Common adverse events in remdesivir treated patients were anemia or decreased hemoglobin (7.9%), AKI, reduced eGFR or CrCl (7.4%), pyrexia (3.3%), hyperglycemia (4.1%), and LFT increases (4.1%). Full data analysis pending further enrollment. (Beigel)
- Randomized open-label, phase 3 trial of 397 hospitalized patients with COVID-19 who received remdesivir for a duration of 5 days v 10 days in 55 hospitals across US, Europe, and Asia. Patients had SpO2 ≤94% on room air, infiltrates on chest imaging, and a positive SARS-CoV-2 PCR within 4 days of enrollment. Patients on mechanical ventilation were excluded. Supportive care was also administered. At baseline patients in 10-day group had significantly worse clinical status (p=0.02) compared to 5-day group. Patients were treated for a median duration of 5 days and 9 days in each group. At day 14, clinical improvement by 2 points, based on 7-point ordinal scale, occurred in 64% of patients treated for 5 days and 54% in those who received 10 days of remdesivir. Median duration of hospitalization among those discharged on or before day 14 was shorter in 5 day group compared to 10 day group (7d v 8d) with more patients being discharged in 5 day group (60% v 52%). Mortality was numerically lower in 5 day group (8% v 11%). Common adverse events were nausea (9%), worsening respiratory failure (8%), elevated ALT (7%), and constipation (7%). (Goldman)

Clinical Trials

- Adaptive COVID-19 Treatment Trial (US - NMH). NCT04280705
- Expanded Access Remdesivir (RDV; GS-5734™). NCT04302766
- Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment (US). NCT04292730
- Study to Evaluate the Safety and Antiviral Activity of Remdesivir in Participants with Severe Coronavirus Disease (COVID-19) (US). NCT04292899

References

- Olender et al. Clinical Infectious Diseases. 24 July 2020. DOI: 10.1093/cid/ciaa1041
- Beigel JH et al. NEJM. 22 May 2020. DOI: 10.1056/NEJMoa2007764
- Goldman JD et al. NEJM. 27 May 2020. DOI: 10.1056/NEJMoa2015301
- Wang Y et al. Lancet. 29 April 2020. DOI: 10.1016/ S0140-6736(20)31022-9

AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Dexamethasone (Decadron®)				
Systemic corticosteroid *Decreases inflammation and production of inflammatory mediators to suppress immune response and pro-inflammatory cytokines associated with COVID-19*	Various dosing regimens have been reported 6 mg PO or IV q24hr for up to 10 days ***Recommended by NIH guidelines for patients on mechanical ventilation (A1) or supplemental oxygen (B1)***	**Should be used on a case-by-case basis weighing patient-specific risk-benefit** **Recommendations**: -Recommended in ICU patients requiring mechanical ventilation or supplemental oxygen >7 days from symptom onset -Consider use in non-ICU patients on supplemental oxygen >7 days from symptom onset -Not recommended in patients not requiring oxygen; less than 7 days from symptom onset; ARDS >14 days from symptom onset	Dexamethasone is 4-5 times more potent than prednisone and has long lasting half-life of 36-54 hours, allowing for self-tapering PO tablet should be given with food to prevent GI upset IV formulation can be given as IV push over 3-5min with concentration of 4-10mg/ml	**AE:** Immunosuppression, metabolic disturbances, hyperglycemia, hypertension, psychiatric disturbances, GI toxicity **Contraindications/Precautions:** risk of secondary infections, activation of latent infections, exacerbation of viral infections due to delayed viral clearance, anaphylaxis

Evidence

- Preliminary report of an open label adaptive RCT (RECOVERY) of hospitalized patients with suspected COVID (89% SARS-Cov-2 positive) in the UK. Patients were randomized in 2:1 ratio to receive either usual care alone (n=4321) or dexamethasone plus usual care (n=2014). Patients received IV or PO dexamethasone 6 mg daily for up to 10 days (median duration 6 days). Patients were stratified by respiratory support received and duration of symptoms. The mean age was 66.1 years and 36% were females. At randomization 16% were on mechanical ventilation or ECMO, 60% were on supplemental oxygen, and 24% were not on oxygen. At least 56% had one coexisting condition. Mortality rate at 28 days was significantly lower with dexamethasone plus usual care (22.9% vs 25.7%, RR 0.83; 95% CI, 0.75 to 0.93; P<0.001). Greatest mortality benefit was among patients on mechanical ventilation (n=1007) (23.3% vs. 26.2%; RR, 0.82; 95% CI, 0.72 to 0.94), with no clear benefit and possibility of harm in those who did not require oxygen (17.8% vs. 14.0%; RR, 1.19; 95% CI, 0.91 to 1.55). Patients with longer duration since symptoms onset (>7 days) had greater mortality benefit with dexamethasone. Patients in the dexamethasone group had a shorter LOS (median 12 days vs 13 days) and were more likely to be discharged alive within 28 days. Less patients in the dexamethasone arm progressed to mechanical ventilation (RR 0.92; 95% CI, 0.84 to 1.01) than in the usual care group. The trial provides evidence supporting the use of dexamethasone in patients requiring oxygen support after 7-14 days of symptoms onset. (RECOVERY)
- CoDex study was a multicenter, randomized, open-label clinical trial of 299 patients in Brazil. COVID-19 patients with moderate to severe disease were randomized (1:1) to receive dexamethasone 20 mg IV daily x5 days, 10 mg of dexamethasone daily for 5 days or until discharge plus standard of care (n=151), or standard of care alone (n=148). Use of dexamethasone resulted in statistically significant increase in the number of ventilator-free days (days alive and free of MV) over 28 days when compared to standard of care alone (6.6 days vs 4.0 days). (Tomazini)

Evidence of other glucocorticoids in COVID-19

- Meta-analysis of 7 randomized trials (n=1703) to evaluate the association between systemic steroids and mortality among critically ill COVID-19 patients. There was minimal heterogeneity between trial results, with the majority of patients from the RECOVERY trial (n=1007). The greatest benefit was seen among patients who received dexamethasone [OR was 0.64 (95% CI, 0.50-0.82; P < .001)]. Administration of systemic corticosteroids, compared with usual care or placebo, was associated with significant reduction in 28-day all-cause mortality (OR 0.66) compared to usual care or placebo. (REACT)
- Randomized clinical trial of 149 ICU patients with acute COVID in France to determine the effect of hydrocortisone on 21-day treatment failure (defined as death or being on mechanical ventilation). The trial was terminated early due failure of hydrocortisone to demonstrate any benefit by day 21 when compared to placebo (42.1% vs 50.7%; P=0.29). (Dequin)
- METCOVID was a parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial evaluating the efficacy of methylprednisolone (MP) among adult hospitalized patients with suspected COVID-19 in Brazil. 416 patients were randomized, and 393 analyzed as mITT (MP=194, placebo=199). Patients in the MP arm received methylprednisolone (0.5 mg/kg) twice daily x5 days. Only 81.3% of patients had PCR confirmed COVID-19. Third (33.8%) were on mechanical ventilation at baseline. Overall 28-day mortality was 37.7%. None of the patients received anti-IL-6, remdesivir or convalescent plasma. The median duration of therapy was 4 days. The rate of 7, 14, and 28-day mortality was similar between groups (placebo 38.2% vs MP 37.1%; P=0.629). Decrease in 28-day mortality was seen in elderly patients >60 yo with high CRP (HR0.634). Increased mortality was observed in patients <60 yo. Patients in the MP arm experienced hyperglycemia requiring more insulin. MP did not affect viral clearance by day 7. (Jeronimo)

Clinical Trials

- Short term corticosteroids in SARS-CoV2 patient (US). NCT04445506
- Dexamethasone and Oxygen support strategies in ICU with COVID-19 PNA (COVIDCUS) (France). NCT04344730

References

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AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Convalescent Plasma				
Plasma, blood product *Plasma derived from recovered donors which has developed humoral immunity, may neutralize SARS-CoV-2 in infected patients*	Managed by individual blood banks 1-2 units once (200-250ml per unit) If a second unit of convalescent plasma is transfused, should be given within 12 hours of completion of first unit administration	**FDA issued Emergency Use Authorization (EUA) for the treatment of hospitalized patients with COVID-19** **Currently unavailable** Largest clinical benefit is associated with high-titer units administered in the early course of disease (≤3 days)	**FDA EUA Fact Sheet for Providers** **FDA Fact Sheet for Patients** **Enrollment in Expanded Access Program (EAP) via Mayo Clinic is no longer available as of 8/28/2020.** **Contact for information:** • NMH: Dr. Ison • LFH: Dr. Tole • CDH: Dr. Manrique • Delnor: Dr. Liu	**AE:** Allergic reactions, viral infections, antibody-mediated enhancement of infection **Precautions:** Transfusion reactions including transfusion-associated acute lung injury or circulatory overload

Evidence

- Observational, open-label study of convalescent plasma expanded access program (EAP) by Mayo Clinic that included 35,322 hospitalized patients with/at risk of severe COVID-19 at 2,807 acute care facilities. Patients received at least one unit of human convalescent plasma donated by COVID-19 survivors. The primary outcome was 7 and 30-day mortality. Half the patients (52.3%) were critically ill, & 27.5% were on mechanical ventilation at baseline. The mortality rate was significantly lower in patients transfused within 3 days of diagnosis when compared to patients transfused 4 days or later. The rate of 7-day mortality was (early transfusion 8.7% vs late 11.9%; P<0.001) and 30-day mortality was (21.6% vs. 26.7%, P<0.0001). Patients who received high IgG plasma had the lowest rate of mortality (8.9%) when compared to medium IgG plasma (11.6%), and low IgG plasma (13.7%), (p=0.048). Reduced mortality was noted with early transfusion and high IgG antibody level transfusion. (Joyner)
- Open-label, multicenter, randomized, controlled trial of 103 patients with confirmed COVID-19 who received convalescent plasma with standard of care (SOC, n=52) compared to SOC alone (n=51) in Wuhan, China. Included patients had severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or mechanical ventilation) COVID-19. Clinical improvement within 28 days, noted as patient being discharged from hospital alive or an observed reduction of 2 points in 6-point disease severity scale was not significantly different among convalescent plasma group compared to SOC (51.9% v 43.1%, p=0.26). Among those with severe disease, significant clinical improvement seen in patients receiving convalescent plasma (91.3% v 68.2%, p=0.03). No significant difference observed in 28-day mortality among patients in each group (15.7% v 24.0%) or a significant difference in time to discharge. Improved negative conversion rate of viral PCR at 72 hrs among those receiving convalescent plasma compared to SOC (87% v 38%, P<0.001). (Li)
- Retrospective, observational study of 21 critically ill patients with COVID-19 who did receive convalescent plasma (n=6) or did not (n=15) in Zhengzhou, China. Death occurred in 5 of 6 patients among those who received convalescent plasma and in 14 of 15 patients who did not (p=0.18). Among those who received convalescent plasma, 50% of patients received 2 transfusions. SARS-CoV-2 clearance was recorded in all patients treated with convalescent plasma on day of transfusion (1 pt), day following transfusion (4 pts), and 3 days following transfusion (1 pt) compared to viral clearance rates of 26.7% among patients who did not receive convalescent plasma. Researchers suggest convalescent plasma may help stop viral shedding and extended survival in patients with COVID-19 and respiratory failure, despite seeing no reduction in mortality rates among critically-ill patients with end stage disease. (Zeng)
- Retrospective, non-randomized case series of 5 critically ill patients with COVID-19 ARDS who were mechanically ventilated and treated with convalescent plasma in Shenzen, China from January to March 2020. All 5 patients were on various antivirals including combination of lopinavir/ritonavir, favipiravir, or interferon alpha-1β in addition to methylprednisolone. Following plasma transfusion which was administered between days 10 and 22 of admission, body temperature normalized within 3 days in 80% (4/5) of patients, SOFA score decreased and PaO_2/FiO_2 increased by day 12 in all patients, and 3 of 5 patients were able to be extubated between 2 to 9 days following transfusion. Two patients remained mechanically ventilated, with one also on ECMO. CRP and IL-6 levels decreased in all patients at day 12. The CT value of patients became negative on day 1 (1 pt), day 3 (2 pts), and day 12 (2 pts). (Shen)

Clinical Trials

- Convalescent Plasma in the Treatment of COVID 19 (US). NCT04343261
- Convalescent Plasma for the Treatment of COVID-19 (US). NCT04389710
- Convalescent Plasma in ICU Patients with COVID-19 induced Respiratory Failure (US). NCT04353206
- Safety in Convalescent Plasma Transfusion to COVID-19 (Mexico). NCT04333355

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- Shen C et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA. 27 March 2020. DOI:10.1001/jama.2020.4783

AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Interferon β-1a (Rebif®)				
Biological Response Modulator *It interferes with viral replication via the interferon-stimulated genes (ISG) and modulates the body's immune response to SARS-CoV-2 infection by increasing the expression of CD-73 protein. It can also reduce ARDS by improving vascular leakage.* EMD Serono	**Trial regimen**: -Interferon beta- 1a: 44 mcg subcutaneous injection every other day for a total of 4 doses (day 1, 3, 5, and 7 while hospitalized)	**Investigational – enrollment in clinical trial-ACTT-III (NMH only): Currently enrolling (remdesivir + interferon beta-1a vs. remdesivir + placebo)** **Per NIH guidelines**: Not recommended for the treatment of severe COVID outside of clinical trials due to lack of benefit and significant toxicities	Monitor CBC, liver function tests, and thyroid function for patients with pre-existing abnormalities. **SubQ administration**: injection site reactions can occur with subcutaneous administration. Monitor patients closely when administering the first injection; doses should be at least 48 hours apart; rotate injection site; do not inject into an area where skin is irritated, red, bruised, or scarred.	**AE:** flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities (leukopenia), hepatotoxicity, and psychiatric symptoms. **Precautions:** use in caution in patients with autoimmune disorders, history of depression, cardiovascular history, or if patients are on chemotherapy and other immunomodulators.

Evidence

- Pre-print: randomized, open-label, controlled trial evaluating the efficacy of IFN β-1a in patients with severe COVID in Iran (n=81). 42 patients were randomized to receive IFN β-1a and 39 patients were in the control group. The mean age in the study was 52 years old. Fifty-two (64.19%) patients had positive nasopharyngeal real-time PCR (RT-PCR) for SARS-CoV-2, and 29 (35.81%) patients were diagnosed according to the clinical signs/symptoms along with the imaging findings. Medan time from symptom onset to IFN administration was 10 days. Forty-percent of patients were on mechanical ventilation at randomization. Almost all patients (79/81) were on hydroxychloroquine. Lopinavir-ritonavir or atazanavir-ritonavir were added to (36/81) for 10 days for patients with severe disease. Corticosteroids were administered to 61.9% of patients in the IFN group and 43.6% of patients in the control group. Corticosteroid dose was equivalent to 250 mg of methylprednisolone for 3 days. In addition, more patients in the IFN group (35.7%) than in the control group (25.6%) received IVIG. As for the primary outcome, time to clinical response was not statistically different between the IFN and control groups (9.7 vs 8.3 days; P 0.95). The six-category ordinal scale was assessed on day 0, 7, 14, and 28 of therapy. On day 7, 19% of patients in the IFN group were discharged with no deaths, but 28% of patients in the control were group were discharged and 25% died. On day 14, discharge rate was statistically higher with IFN (IFN 66.7% vs. control 43.6%; OR, 2.5; 95% CI, 1.05 to 6.37). The 28-day mortality was significantly lower with IFN (19% vs. 43.6%; P=0.0015). Analysis showed that early administration of IFN had significantly reduced mortality (OR, 13.5; 95% CI, 1.5 to 118). Injection related side effects happened in 19% of IFN patients, and 4 patients experiences neuropsychiatric problems (agitation and depression). (Davoudi-Monfared).

Interferon Beta -1b:

- An open-label, Phase 2 clinical trial randomized 127 participants (2:1) to combination antiviral therapy or lopinavir/ritonavir. In the combination antiviral therapy group, the treatment regimen differed by time from symptom onset to hospital admission. Participants hospitalized within 7 days of symptom onset (n = 76) were randomized to triple drug therapy (interferon beta-1b 8 million units administered subcutaneously every other day for up to 7 days total, lopinavir/ritonavir, and ribavirin); those hospitalized ≥7 days after symptom onset (n = 51) were randomized to double therapy (lopinavir/ritonavir and ribavirin) because of concerns regarding potential inflammatory effects of interferon. Patients in the control group received lopinavir/ritonavir alone regardless of the time from symptom onset to hospitalization. The study participants were patients in Hong Kong with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who were hospitalized until they had two negative nasopharyngeal (NP) swab tests. The time to a negative result on PCR SARS-CoV-2 test on an NP swab (the primary endpoint) was shorter in the combination therapy group than in the control group (median of 7 days vs. 12 days; P = 0.001). The combination group had more rapid clinical improvement as assessed by the National Early Warning Score (NEWS) 2 and Sequential Organ Failure Assessment (SOFA) score and a shorter hospital stay (median of 9 days for the combination group vs. 14.5 days for the control group; P = 0.016). There was no difference in oxygen use between the groups. The antiviral and clinical effect was more pronounced in the patients hospitalized within 7 days of symptom onset, suggesting that interferon beta-1b with or without ribavirin was the critical component of the combination antiviral therapy. The study provides no information about the effect of interferon beta-1b when administered ≥7 days after symptom onset. (Hung)

Clinical Trials

- Adaptive COVID-19 Treatment Trial 3 (ACTT-3). NCT04492475
- Click for more ongoing clinical trials for interferon and COVID-19

References:

- Davoudi-Monfared et al. Antimicrob Agents Chemother. 13 July 2020. DOI: 10.1128/AAC.01061-20
- Hung et al. Lancet. 8 May 2020. https://doi.org/10.1016/S0140-6736(20)31042-4

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Sarilumab (Kevzara®)				
IL-6 receptor antagonist; Humanized monoclonal antibody *Binds to soluble membrane-bound IL-6 receptors to inhibit IL-6 mediated pro-inflammatory response* Sanofi-Regeneron	Trial Regimens: • Sarilumab 400 mg IV once • Placebo IV once Consider redosing 24hr after initial dose if no clinical response – up to 1 additional dose Repeat weekly dosing is permitted for patients requiring supplemental oxygen per trial protocol, up to a maximum of 6 total doses	**Investigational – US clinical trial stopped in light of recent sarilumab RCT results demonstrating no significant clinical benefit and potential risk for adverse events** Hospitalized patients on mechanical ventilation with critical COVID-19	Consider checking inflammatory markers (D-dimer, CRP, ESR, ferritin, fibrinogen) prior to administration Consider checking for history or evidence of tuberculosis prior to initiation	**AE:** increased serum ALT and AST, antibody development, local injection site reaction, neutropenia **Contraindications/Precautions:** GI perforation, neutropenia, thrombocytopenia, hepatotoxicity, hyperlipidemia, infusion reactions, infection, tuberculosis

Clinical trial no longer active in US based on preliminary results which did not demonstrate significant reduction in CRP nor clinical improvement compared to supportive care

Evidence

- Press Release from Sanofi-Regeneron – Compared to placebo, sarilumab 400mg use among mechanically ventilated patients with critical COVID-19 did not meet its primary endpoint of significant reduction in CRP levels nor key secondary endpoints including 1-point clinical improvement based on 7-point ordinal severity scale. This was in combination with supportive care. Adverse events were experienced at high rates, 80% in sarilumab arm & 77% among those receiving placebo, including serious AE such as multiorgan dysfunction syndrome (6% sarilumab, 5% placebo) and hypotension (4% sarilumab, 3% placebo). Based on these results, the trial has been stopped in the US, including a secondary cohort of patients receiving sarilumab 800mg. (Sanofi-Regeneron)
- Preliminary analysis of phase II trial comparing sarilumab 200mg v 400mg v placebo in COVID-19 patients with baseline categorization of severe (dyspnea, hypoxia, or >50% lung involvement on imaging), critical (respiratory failure, shock, or multi-organ failure), or multi-system organ dysfunction. Among 358 patients included in the trial, administration of sarilumab was associated with drastic reduction in CRP levels from highest baseline (-79% with 400mg dose, -77% with 200mg, -21% with placebo). In an exploratory analysis, sarilumab had no notable benefit when combining severe and critical subgroups, due to negative trends seen within the severe group. In the critical subgroup all exploratory outcomes were positive, with notable benefit in the 400mg dose compared to placebo (endpoints: died or on a ventilator 32% v 55%, 2-point clinical improvement on 7-point ordinal scale 59% v 41%, off oxygenation 58% v 41%, discharged 53% v 41%). As a result, the phase III trial will explore use of sarilumab 400mg dose v placebo in the critical study population.

Clinical Trials

- Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19. NCT04315298 (NMH) - stopped
- Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial - CORIMUNO-19 - VIRO. NCT04341870
- Sarilumab COVID-19. NCT04327388
- Anti-il6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure. NCT04322773
- Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia. NCT02735707

References:

- Press: Sanofi and Regeneron – Clinical Trial Stop (Announcement 7/2/20)
- Press: Sanofi and Regeneron Update (Announcement 3/16/20 & Announcement 4/27)
- Kevzara [Package Insert]

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Tocilizumab (Actemra®)				
IL-6 receptor antagonist; Humanized monoclonal antibody *Binds to soluble membrane-bound IL-6 receptors to inhibit IL-6 mediated pro-inflammatory response*	Various dosing regimens have been reported 400mg IV once **OR** 8mg/kg* IV once, up to 800mg Consider redosing 8-24hr after initial dose if no or partial clinical response – up to 2 additional doses *Weight-based Dose rounding: • 50-60 kg: 400mg • >60-85 kg: 600mg • >85 kg: 800 mg Dosing adjustments for hepatic impairment	**Not recommended outside of investigational use due to lack of efficacy in a recent clinical trial** Hospitalized patients with severe COVID-19 IL-6 receptor antagonists have unclear place in therapy in light of recent sarilumab RCT results demonstrating no significant clinical benefit and potential risk for adverse events	Consider checking inflammatory markers (D-dimer, CRP, ESR, ferritin, fibrinogen) prior to administration Consider checking for history or evidence of tuberculosis prior to initiation	**AE:** Increased ALT/AST, neutropenia, thrombocytopenia, injection site reaction, Upper respiratory tract infections, nasopharyngitis, headache, hypertension **Contraindications/Precautions:** risk of serious and fatal infections, including tuberculosis, invasive fungal infections, viral infections, and PJP. Increased risk of gastric perforation, hepatic injury

Evidence

- Meta-analysis of 10 observational studies (n=1358) showed that mortality was 12% lower for COVID-19 patients treated with tocilizumab compared to control. The suggested number needed to treat was 11. There was no mortality benefit in patients who received tocilizumab + steroids. These results carry a high risk of bias driven by heterogenic observational studies with unmatched cohorts. Results must be interpreted with caution. (Malgie)
- Press release: Roche announced that the phase III EMPACTA study met its primary endpoint, showing that patients with COVID-19 associated pneumonia who received tocilizumab plus standard of care were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care (P-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]). The cumulative proportion of patients who progressed to mechanical ventilation or death by day 28 was 12.2% in the tocilizumab arm vs 19.3% in the placebo arm. The difference in time to hospital discharge (6 vs 7.5 days) or time to improvement in clinical status (6 vs 7 days) was not significant. The EMPACTA study did not identify any new safety signals for tocilizumab. (Roche)
- Pre-print: COVACTA study was a phase III randomized, double-blind, placebo controlled study investigating the efficacy and safety of tocilizumab compared to placebo in hospitalized patients with severe COVID. The primary endpoint was measured using 7-category ordinal scale of clinical status based on need for supplemental oxygen at day 28. 452 hospitalized patients were randomized (2:1) to tocilizumab (8 mg/kg) (n=294) and placebo (n=144). There was no difference in primary endpoint of improved clinical status (OR 1.19; P 0.36), or secondary end point of difference in patient mortality at week four (Toci 19.7% vs placebo 19.4%; P=0.941). However, hospital discharge was 8 days shorter with tocilizumab (20 days) than placebo (28 days); P=0.037. Serious adverse events occurred in 34.9% of patients in the tocilizumab arm and 38.5% of patients in the placebo arm. Rate of infections were similar (Toci 38.3% vs. placebo 40.6%). (Rosas)
- Retrospective observational cohort study of 630 ICU patients at 13 hospitals in NJ, USA (toci= 210, control= 420). The primary end-point was hospital -related mortality. Over-all mortality rate in the study was 57%. There was less mortality in the tocilizumab treated patients (toci 49% vs control 61%). Tocilizumab was associated with decreased hospital-related mortality using primary multivariable cox regression analysis with propensity matching (HR 0·64, 95% CI 0·47–0·87; P=0·0040). Largest benefit was observed in patients on mechanical ventilation with CRP value of 15 mg/dl or higher. (Biran)
- Single-center cohort study of 154 patients (tocilizumab=78, control=76) to assess the effectiveness and safety of tocilizumab in mechanically ventilated patients with COVID-19. Tocilizumab-treated patients were younger (55 vs 60 years), had less COPD (10% vs 28%) and lower D-dimer (2.4 vs 6.5). Tocilizumab was associated with a reduction in mortality [(HR 0.55 (95% CI 0.33, 0.90)]. However, patients who received tocilizumab were more than twice as likely to develop a superinfection (54% vs. 26%; p<0.001), mainly ventilator associated pneumonia (45% vs. 20%; p<0.001). Staphylococcus aureus accounted for ~50% of bacterial pneumonia. (Somers)

Clinical Trials

- Favipiravir combined with tocilizumab in the treatment of COVID-19. NCT04310228
- Tocilizumab vs CRRT in management of cytokine release syndrome (CRS) in COVID-19 (TACOS). NCT04306705
- Tocilizumab to Prevent Clinical Decompensation in hospitalized, non-critically ill patients with COVID-19 pneumonitis (COVIDOSE). NCT04331795
- A study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia (COVACTA) NCT04320615
- Tocilizumab in COVID-19 Pneumonia (TOCIVID-19). NCT04317092
- Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of COVID-19. NCT04332094
- Efficacy of Early Administration of Tocilizumab in COVID-19 Patients. NCT04346355
- Efficacy and Safety of Tocilizumab in the Treatment of SARS-Cov-2 Related Pneumonia NCT04332913

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AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Canakinumab (Ilaris®)				
IL-1β receptor antagonist; Monoclonal antibody *Binds to IL-1β to block interaction between IL-1β and IL-1 receptor, leading to inhibition of IL-1β induced gene activation and production of downstream inflammatory mediators including IL-6 and CRP and potentially preventing inflammatory damage associated with ARDS* Novartis	Trial Regimens: • Canakinumab dosed based on pt's body weight • 40-59.9kg: 450mg • 60-80kg: 600mg • >80kg: 750mg • Placebo	**Investigational – enrollment in clinical trial is currently closed**	Recommended for patients to have up to date immunizations including pneumococcal and influenza vaccines before initiating therapy. Avoid administration of live vaccines in patients receiving concurrent therapy.	**AE:** increased risk of infections, particularly upper respiratory tract infections, nasopharyngitis, ALT/AST elevations, GI toxicity including diarrhea, abdominal pain, nausea, headache, weight gain **Contraindications/Precautions:** Neutropenia, thrombocytopenia, infections, Macrophage activation syndrome, malignancy, tuberculosis, hypersensitivity, infusion reactions
Clinical trial enrollment is currently closed				
Evidence • No evidence currently available – clinical trials pending Clinical Trials • Study of Efficacy and Safety of Canakinumab Treatment for CRS in participants with COVID-19 induced pneumonia (US – NMH). NCT04362813 • Observation Study, Use of Canakinumab administered subcutaneously in the treatment of COVID-19 pneumonia (Italy). NCT04348448 • Canakinumab to reduce deterioration of cardiac and respiratory function due to COVID-19 (US). NCT04365153				
References: • Ridker PM et al. NEJM. 21 September 2017. • Ilaris [Package Insert]				

AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Baricitinib (Olumiant®)				
Janus Kinase Inhibitor *Inhibition of JAK1/2 to potentially mediate cytokine signaling involved in inflammation; Inhibition of cyclin G-associated kinase to regulate endocytosis; interrupt viral entry and viral particle assembly via disruption of AP2-associated protein kinase 1 (AAK1)*	Trial Regimens: • Baricitinib 4 mg PO daily for duration of hospitalization, up to 14 days • Placebo PO daily Used in combination with standard of care remdesivir per study protocol	**Investigational – enrollment in clinical trial (NMH only): Currently closed**	Available as 2mg tablets, patients will be given 2 tablets for each admin Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH List 2016) Caution in patients with soy allergies as tablet contains soybean lecithin	**AE:** upper respiratory infections, nausea, headache, nasopharyngitis, dyslipidemia, AST/ALT elevations**,** herpes virus infections **US boxed warning** for risk of developing serious infections (active TB, invasive fungal, bacterial, or viral infection), lymphoma/malignancy, thrombosis including DVT/PE **Contraindications/Precautions:** hematologic toxicity (lymphopenia, anemia, neutropenia), hepatotoxicity, GI perforation

Evidence

- Single-center, observational study of 15 patients in US with moderate COVID-19 requiring hospitalization and supplemental oxygen who received baricitinib 2-4mg in combination with hydroxychloroquine 200-400mg daily. 60% of patients required ICU-level care with 26.7% requiring mechanical ventilation, with durations ranging from 6-20 days. All patients had elevated inflammatory markers (CRP, IL-6, ESR) at baseline. 86.7% of patients had significant reduction in body temperature and CRP levels over course of therapy, and 73.3% had clinical improvement in oxygen requirement. 80% of patients were deemed to be recovered due to resolution of oxygen requirement and cessation of continued medical care. Three patients died and two additional patients developed secondary bacterial or fungal infections requiring prolonged ICU stay. (Titanji)
- Machine learning identified baricitinib as a potential agent to block the viral infection process caused by SARS-CoV-2 by reducing the ability of the virus to infect lung AT2 alveolar epithelial cells in the lung via disruption of AAK1 kinase and binding to G-associated kinase, members of the numb-associated kinase (NAK) family.
- Mechanism of baricitinib has potential to impair SARS-CoV-2 endocytosis and early stages of viral spread, as well as inhibit the signaling of several cytokines involved in cytokine storm including IL-6, IL-1β, and IL-12. IL-4 and IFN-γ, two cytokines who rely on JAK for signaling, inhibit ACE2 expression in vitro demonstrated reduction of infection, replication, and excretion of SARS-CoV-2.

Clinical Trials

- Baricitinib Therapy in COVID-19 (Italy). NCT04358614 - Completed, pending results
- Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in hospitalized patients (Canada). NCT04321993
- Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot study. (BARI-COVID) (Italy). NCT04320277
- Safety and Efficacy of Baricitinib for COVID-19 (US). NCT04340232
- Efficacy and Safety of Novel Treatment Options for Adults with COVID-19 Pneumonia (CCAP) (Denmark). NCT04345289

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AGENTS	RECOMMENDED DOSE	PLACE IN THERAPY	OPERATIONS	CONTRAINDICATIONS/ADVERSE EVENTS
Hydroxychloroquine (HCQ)				
Antimalarial *Increases pH of acidic intracellular vesicles that may lead to inhibition of endosome-mediated fusion, viral entry and pH dependent steps in viral replication. Anti-inflammatory and immunomodulatory properties that may inhibits release of inflammatory cytokines INFγ, IL-6, IL-1, TNF-α* HCQ: Hydroxyl analog of chloroquine. Similar activity and properties to chloroquine w/ ↓tox	Various dosing strategies have been reported: 400mg PO BID on day 1 then 200mg PO BID x 4 days **OR** 600mg PO BID on day 1 then 200mg TID x 4 days **FDA EUA no longer available**	**Not recommended for COVID-19 due to lack of definitive evidence differentiating outcomes benefit with HCQ compared to supportive care and increased risk of adverse events** Not recommended outside of clinical trials, due to concerns about safety and efficacy FDA cautions against use for COVID-19 outside of hospital setting or clinical trial	**Avoid use with concurrent azithromycin (esp in pts with acute renal failure) due to QTc prolongation and risk of cardiac arrhythmias (Chorin, NIH Guidelines)** For patients with underlying CV disease or on concurrent QT prolonging medications, obtain baseline EKG and monitor QTc. Avoid use if baseline QTc ≥ 500ms or in pts with known congenital QT prolongation. Maintain electrolytes (K>4mEq/L, Mg>2mg/dl) while on therapy (Roden) **Do not crush tablet** → order as oral suspension for patients without PO access, can be given via tube. Mixing instructions for oral suspension available Monitor for drug-drug interactions, WBC Food can increase bioavailability (CQ)	**AE:** QT prolongation, nausea, vomiting, cardiomyopathy, pancytopenia, hepatotoxicity, irreversible retinopathy, extrapyramidal reaction, pruritus **Contraindications/Precautions:** Caution in pts with QT prolongation, underlying cardiac disease, seizure history, severe hypoglycemia, proximal myopathy or neuromyopathy, retinal toxicity, GI disorders, hepatic impairment, G6PD deficiency Signs of overdose (> 3-6g CQ): hypotension, tachycardia, bradycardia with atrioventricular block and electrolyte disturbances Drug-drug interaction checker available here

Evidence

- Randomized, double-blind, placebo-controlled trial of hydroxychloroquine post-exposure prophylaxis among 821 asymptomatic patients who were not hospitalized and reported to be at high-risk exposure to a confirmed COVID-19 contact. Pts were enrolled within 4 days following potential exposure and received HCQ 800mg once followed by 600mg once 6-8 hours later, then 600mg daily for 4 additional days or placebo. Primary outcome of incidence of lab-confirmed COVID-19 or clinically-suspected COVID-19 within 14 days did not differ significantly among those receiving HCQ v placebo (11.8% v 14.3%). Side effects were more common with HCQ than placebo (40.1% v 16.8%) without any reports of serious adverse events. (Boulware)
- Randomized, parallel-group trial to evaluate the efficacy of HCQ (400mg/day; 200mg BID x 5 days) v standard treatment (supportive care=control) in 31/62 patients with mild COVID-19 illness (excluded severe/critically ill) in Wuhan. Time to clinical recovery (TTCR) in days, clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment. Fever recovery time (3.2d vs. 2.2d, p=0.0008) and duration of cough (3.1d vs. 2d, p=0.0016) significantly shortened in HCQ versus control group, respectively; per chest CT, pneumonia improved 25/31 (80.6%) in HCQ vs. 17/31 (54.8%) in control group, p=0.047. Severe illness progressed in 4 of 62 patients (all controls). Mild adverse reactions (HCQ): rash, headache. (Chen Z)
- Pre-print information: Non-randomized propensity-matched comparative study of pts receiving HCQ 600mg daily within 48hrs of hosp (n=84) v those who did not (control, n=97) combined with standard of care. Among 181 pts, all of whom had bilateral PNA and required supplemental oxygen, no difference found in the composite outcome of transfer to ICU within 7 days or all-cause mortality (HCQ 20.2% v control 22.1%). ARDS developed within 7 days in 27.7% of pts treated with HCQ v 24.1% in controls. 9.5% of pts in HCQ group experienced EKG changes requiring therapy discontinuation, with a median d/c time of 4 days. Authors stated findings do not support use of HCQ in COVID PNA. (Mahévas)
- Pre-print information: Multicenter, open-label RCT of 150 pts hospitalized with COVID-19 who received HCQ 1,200mg daily x 3 days followed by 800mg daily + SOC (n=75) v SOC alone (control, n=75). 28-day negative conversion rates of SARS-CoV-2 was not different between HCQ + SOC v controls (85.4% v 81.3%, median time to negative conversion 8 v 7 days) nor were differences in negative conversion rates at days 4, 7, 10, 14, 21, including in a sub-analysis of pts who received HCQ within 7 days of symptom onset v those with initiation beyond 7 days. No difference in 28-day symptom alleviation (59.9% v 66.6%), however in a post-hoc analysis in which confounding use of other antiviral agents were removed, HCQ was associated with an improved rate of symptom alleviation, more rapid normalization of CRP, and a trend towards more rapid recovery of lymphopenia. AE rate of 30% in HCQ (10% diarrhea) v 8.8% in controls. (Tang)
- Pre-print information: Retrospective review of 84 adult pts with COVID-19 in US treated with HCQ and azithro combination therapy, which found a significant association with QTc prolongation (30% of pts with increase >40ms, 11% of pts with increase to >500ms), placing these pts at higher risk for arrhythmias, although no cases of torsades reported. Maximal QTc increase was noted on treatment days 3-4. Acute renal failure was noted to be a significant predictor of severe QTc prolongation, but baseline QTc and QTc >460ms did not predict QTc prolongation. Concurrent amiodarone use associated w/ risk. Authors recommend repeat monitoring of QTc for pts receiving HCQ/Azithro combo. (Chorin)
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