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**VHA PBM Draft Literature Summary on Investigational and off-label Medications for COVID-19**

**What's New in COVID-19 Pharmacologic Treatment and Prevention? *Short summary of new literature 6/1/20-6/7/20***

**Remdesivir**

- A [press release from Gilead on 6/1/20](#) released data from the SIMPLE trial of patients with **moderate** COVID, comparing 5 or 10 days of Remdesivir or standard care.
- Topline results showed that 5 days of Remdesivir was superior to standard care in proportion of patients with clinical improvement at day 11 (at least 1 point improvement on ordinal scale), occurring in 76% of those on 5 days Remdesivir, 70% with 10 days, and 66% with standard care. 10 days of therapy was numerically but not statistically better than standard of care. The study is continuing to expand to include more patients and increase study power, but results are difficult to interpret, as 5 days of therapy but not 10 provided statistically significant benefit.
  - At least 1 point worsening on ordinal scale occurred in 3% of 5 day, 6% of 10 day and 11% of standard care patients: death occurred in 0, 1% and 2%
  - Adverse events that were at least grade 3 occurred in 10% of 5 day, 11% of 10 day and 12% of standard care patients. The most common adverse events in both groups were nausea, diarrhea and headache
- This study does suggest 10 days of therapy is not likely to be more efficacious than 5 days with moderate illness, supporting the shorter duration of therapy in less severely ill patients

**Chloroquine/Hydroxychloroquine (CQ/HCQ)**

- A randomized, placebo controlled trial of hydroxychloroquine as post-exposure prophylaxis failed to show benefit, with illness compatible with COVID-19 developing in 11.8% of HCQ and 14.3% of placebo patients, but was associated with a significantly greater incidence of adverse events, especially gastrointestinal side effects.<sup>23</sup>
- 2 negative studies on use of HCQ as treatment for COVID-19 were retracted, one from NEJM and one from Lancet, as data was questioned and the authors could not verify the patient level data from the Surgisphere database and data were questioned based on published statistics. Meanwhile, the HCQ arm of the randomized [RECOVERY trial](#) was dropped when an interim analysis ruled out any meaningful benefit on mortality, hospital length of stay or other outcomes.
- On June 15<sup>th</sup>, the US FDA [revoked the Emergency Use Authorization for HCQ/CQ](#), citing that in light serious cardiac and other adverse events, the known and unknown potential benefit no longer outweighs the potential risks for authorized use

**Anticoagulation**

- The CHEST consensus panel developed a guideline and expert panel report on the [prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19](#)<sup>4</sup> with guidance that differs slightly from the NIH COVID-19 guidelines, but largely recommends current standard of care treatments given a lack of evidence for alternative strategies (such as higher dose anticoagulation as prophylaxis or extended prophylaxis after discharge)

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

- This set of guidelines adds to additional updates in the NIH DHHS COVID-19 Guidelines, as well as those from the [American Society of Hematology](#) and the [Anticoagulation Forum Group](#)

**Guidelines, Clinical Recommendations and Other Important links on Treatment of COVID-19**

- **Separate treatment guidance from the CDC, IDSA and NIH/DHHS note the limited evidence to support investigational and off-label therapeutics for treatment of COVID-19, and recommend that these treatments be studied in well-designed controlled clinical trials whenever possible. The DHHS panel acknowledges, however that many patients and providers may be seeking guidance and may not have access to clinical trials.<sup>1,2,3</sup>**
  - [NIH COVID-19 Treatment Guidelines<sup>2</sup>](#)
  - [Interim Clinical Guidance for Management of Patient with confirmed COVID-19<sup>1</sup>](#): Centers for Disease Control and Prevention (CDC)
  - [Guidelines from the Infectious Diseases Society of America<sup>3</sup>](#) published April 11, 2020
- The FDA released a [drug safety communication on 4/21/20 cautioning against the use of CQ or HCQ in the outpatient setting](#) and recommend they only be used for the treatment of COVID-19 in the setting of a clinical trial or in hospitalized patients per the FDA 3/28/20 [Emergency Use Authorization for CQ or HCQ for COVID-19](#). On June 15<sup>th</sup>, in light of additional data on adverse events, and negative clinical efficacy, the [FDA revoked the EUA](#), citing criteria were no longer met to warrant it.
- An expert CHEST consensus panel has developed guidelines for the prevention, diagnosis and treatment of venous thromboembolism in COVID-19.<sup>4</sup>
- The FDA released an [Emergency Use Authorization for use of remdesivir](#) in hospitalized patients with severe COVID-19 infections in the U.S. on 5/1/20
- **In the absence of a clinical trial, any decision to consider off-label therapies in VHA be in keeping with the PBM Document entitled: [Pharmaceutical Use Outside of Approved Indications Guidance on “Off-Label” Prescribing \(August 2013\)](#). Decisions should be in consultation with facility experts, customized to the needs of the patient and carefully considering potential benefits and harms. Discussion of these risks/benefits should be clearly communicated to the patient and/or family as part of the decision prior to proceeding with off-label therapy.**
- Please note this information is changing very rapidly and should be considered as updated as the current date of the document

## **Investigational and Off-Label Therapies under Evaluation for Treatment of COVID-19**

**REMEDESIVIR:** *Granted [an Emergency Use Authorization \(EUA\)](#) by the FDA on 5/1/2020 for treatment of hospitalized patients with severe COVID-19 (e.g. those requiring supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO), or those with a room air oxygen saturation  $\leq 94\%$ ). Gilead is donating their initial supply of medication to the Federal Government and the distribution is being coordinated through AmerisourceBergen. Additional documents prepared by the FDA include a [Fact Sheet for Patients and Caregivers](#), and a [Fact Sheet for Health Care Providers](#) (in place of traditional prescribing information).*

- Nucleotide prodrug antiviral with broad activity against several families of viruses, including the coronaviruses that cause Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome MERS <sup>5,6,7,8,9</sup> Animal data as both prophylaxis and treatment of MERS showed positive results<sup>7</sup>
- Completed early clinical trials for Ebola, including pharmacokinetic and limited safety data but was less effective than other treatment options
- Good in vitro activity against COVID-19<sup>5</sup>
- **Clinical trials ongoing in the U.S. for hospitalized patients with COVID-19:**
  - **Compassionate use administration** (see table 1) in hospitalized patients: improvement was 68%, mortality 13% and 47% had been discharged at the date of their last follow-up<sup>10</sup>
  - **Randomized, placebo-controlled trial in China** halted prematurely when epidemic controlled, making further recruitment difficult<sup>11</sup>
    - Underpowered for primary endpoint but did not show significant difference in time to clinical improvement, mortality, time to reduction of viral load or other secondary clinical endpoints, although positive trends seen in some cases
    - No significant safety signals other than rash (7% vs. 3% and thrombocytopenia 10% vs. 6%)
  - **Results of NIAID ACTT-1 Trial** of 1063 hospitalized patients with COVID-19 found remdesivir superior to placebo in time to clinical recovery: 11 days vs. 15 days (rate ratio for recovery 1.32, 95% CI 1.12 to 1.55,  $p < 0.001$ ) and trend towards decreased mortality: 7.1% vs. 11.9% (HR for death 0.7, 95% CI 0.47 to 1.04,  $p = 0.059$ )<sup>12</sup>. All patients were treated for 10 days. These data led to the FDA EUA of remdesivir.
    - The benefit was statistically significant only in the group of patients who required supplemental oxygen at baseline, but not in those who were less ill, or those requiring invasive or non-invasive mechanical ventilation, suggesting the group most likely to benefit from treatment with remdesivir in addition to standard care
    - The FDA EUA suggests patients who are not severely ill could be considered for treatment with 5 days of therapy, to be extended if they do not show clinical improvement, based on topline results from the SIMPLE trial that did not show a difference in clinical improvement with 10 vs. 5 days of remdesivir in severe COVID-19), but without a control group, it is unclear exactly what efficacy remdesivir holds in severely ill patients.<sup>13</sup> [Another press release from 6/1/20](#) included topline results from the phase 3 SIMPLE trial of moderately ill patients, which included a standard of care arm. In this study – 5 days but not 10 days, was associated with improvement in ordinal score at day 11 versus standard of care. This supports the shorter treatment duration in moderately ill patients.
    - Most common adverse events included increased transaminases, rash, diarrhea, renal impairment and hypotension.
  - Dose is 200mg IV once followed by 100mg IV daily. The FDA EUA suggests 5 days of therapy for those not requiring mechanical ventilation (with the option to extend up to 5 additional days for patients who do not respond) and 10 days of therapy for those on mechanical ventilation or ECMO
  - Uncontrolled safety data from phase 1 trials and compassionate use data for treatment of Ebola primarily demonstrated reversible grade 1 and 2 elevations of AST or ALT.<sup>14</sup> In the ACTT trial, serious adverse events occurred in 21% of remdesivir and 27% of placebo patients with only 2 reactions in each group felt to be study related.<sup>11</sup> Most adverse events were not significantly different from placebo, including acute kidney injury (0.7% remdesivir vs. 1.3% placebo) or increased transaminases (0.6% vs. 1.1%). Hypotension was recorded in 2.2% of those receiving remdesivir and 1.3% of patients receiving placebo

### CHLOROQUINE / HYDROXYCHLOROQUINE (CQ/HCQ)

- Antimalarial drugs with nonspecific activity against several coronaviruses, including in vitro activity vs. COVID-19.<sup>15,16</sup> An [Emergency Use Authorization \(EUA\) was issued](#) by the FDA for the use of CQ or HCQ as treatment for COVID-19 infections on 3/28/20 subject to specific criteria and when issued by a valid prescription. A recent [FDA Safety briefing cautions against the use of HCQ or CQ outside of a clinical trial or hospital setting due to arrhythmia risk](#). The NIH Treatment Guidelines were updated on 6/11/20 and now recommend AGAINST the use of HCQ or CQ except in the context of a clinical trial and recommend against high dose CQ or the combination of HCQ and azithromycin due to toxicity and on June 15<sup>th</sup>, the FDA revoked the EUA citing limited clinical data on effectiveness, but significant risk of cardiac and other adverse events.
- **Data to support use of HCQ or CQ as treatment of COVID-19 is limited and conflicting (Table 1). Emerging data regarding cardiac involvement with COVID-19 requires caution with use of CQ and HCQ, and close monitoring of QTc if used (see table 3).**
  - Current data limited to case series, small open-label randomized controlled trials, and retrospective cohort studies. Each study has significant limitations and may not be powered to identify differences in rare adverse events. See Table 1 for more information
  - **Virologic outcomes:** Of 3 evaluating impact of CQ/HCQ on virologic outcomes, only one showed reduction in time to negative viral PCR for COVID-19 which has since been highly criticized for excluding several patients in HCQ arm who had poor outcomes.<sup>17,18,19,20,31</sup> The study that showed a positive result also suggested that HCQ in combination with azithromycin was associated with more rapid reduction of viral load, but has been since widely criticized.
  - **Clinical outcomes:** of 3 randomized trials and 4 retrospective observational cohorts with varying statistical controls for confounding of CQ/HCQ, in only 1 of the randomized trials was HCQ associated with 1 day less of fever and cough while the other trials (including the largest of 150 patients) did not find a difference in clinical outcomes between those who received CQ/HCQ vs. standard care.<sup>16,17,18,21,22,23,24</sup> The retrospective cohort studies with propensity score adjustments did not find association between HCQ and risk of progression to mechanical ventilation/intubation, or a composite of intubation or death. One study did find an increased risk of death from any cause in patients who received HCQ but should be viewed as preliminary.<sup>19-22</sup>
  - **Prophylaxis:** a large, randomized, placebo controlled trial in over 800 patients with high risk exposure to COVID-19 (occupational or household contact) failed to show benefit but was associated with significantly more adverse events.<sup>25</sup> In this trial, participants were given 5 days of HCQ who were enrolled within 3-4 days after exposure. Of the 414 patients who received HCQ, 11.8% developed COVID-19 compatible illness, compared with 14.3% of 407 placebo patients. Adverse events were significantly more common with HCQ, especially nausea (23% vs. 8%), and diarrhea/abdominal pain/vomiting (23% vs. 4%)
- **Safety / adverse events:**
  - While generally well tolerated when used as malaria prophylaxis (CQ/HCQ) or chronically for rheumatoid arthritis or lupus (HCQ), do have a narrow therapeutic index with 6 grams being a fatal dose in an adult. HCQ is generally felt to be safer than CQ. Patients with COVID-19 may have additional risk factors, such as myocardial involvement of COVID-19, electrolyte disturbances, and other medications that may increase risk of adverse events to CQ/HCQ.
    - QT prolongation with QTc  $\geq$  10-35% in several case series, including rare cases of ventricular arrhythmia<sup>26,27,28,29,30</sup>
    - Appears dose dependent and greater when combined with azithromycin, and cardiovascular manifestations of COVID-19 may contribute to the risk
    - All patients should have an EKG prior to administration of HCQ and CQ and during therapy to assess effect of the medication.
  - **Other side effects to monitor include** rash - a case of drug reaction with eosinophilia and systemic symptoms- DRESS, and one severe exacerbation of psoriasis have been reported, central nervous system (seizures), gastrointestinal and hematologic effects (hemolytic anemia), weakness, and hypoglycemia
  - Both can inhibit CYP2D6 and result in drug interactions with other common medications so this should be checked also prior to initiation (e.g. beta-blockers)

### Lopinavir/ritonavir (Lop/rit)

- Commercially available antiviral for the treatment of HIV with In vitro activity against several coronaviruses, including SARS, MERS and COVID-19
- **Early in China, many patients treated empirically with lop/rit, but efficacy data is lacking and best evidence does not support use in patients with severe COVID**
  - Data from the first randomized controlled trial of lop/rit vs. control in 199 patients with severe COVID for 14 days did not show benefit in reducing time to clinical improvement or negative viral PCR for COVID and was associated with an increased risk of gastric adverse events<sup>31</sup>
  - **Recent study of combination of Lop/rit + ribavirin and interferon beta-1b vs. Lop/rit alone** in patients with mild/moderate COVID-19 suggested some benefit on clinical and virologic outcomes, but given known side effect profile of interferons and ribavirin and very rapid results demonstrated, role of this therapy remains to be defined further<sup>32</sup>
- **Doses have ranged from 400mg/100mg to 400mg/200mg twice daily of lop/rit**
  - Note crushing of tablet may reduce bioavailability by 50%<sup>33</sup>
- **Gastrointestinal tolerance** may be a significant issue – in one report of use in 5 patients with COVID-19, nausea, vomiting or diarrhea developed in 4 of 5 and increased liver enzymes in 3 of 5 although causality unclear
- **Drug-drug interactions are common with lop/rit, including medications that are contraindicated. Like HCQ/CQ and azithromycin, lop/rit can prolong the QTc. A pharmacist should review the patient's medication list for drug interactions and necessary adjustments prior to initiation**

### Darunavir +/- ritonavir or cobicistat (DRV/r, DRV/c)<sup>34</sup>

- Press release on J&J.com states Janssen has NO clinical NOR pharmacological evidence to support inclusion of DRV/cobicistat in treatment guidelines for COVID-19, nor are there published data on safety and efficacy of DRV, DRV/c or DRV/c/emtricitabine/tenofovir alafenamide for treatment of COVID-19
- **They also report – unpublished in vitro data suggest DRV is UNLIKELY TO HAVE SIGNIFICANT ACTIVITY VS. COVID-19 AT SAFE/EFFICACIOUS DOSES**
- **Finally, they refer to a single-center open-label randomized controlled trial from China of DRV/c in 30 patients that showed DRV/c was NOT EFFECTIVE**
- **Based on available evidence, DRV, DRV/c and DRV/r are NOT recommended to treat COVID-19 at this time**

### Other agents studied as therapeutic agents in patients with severe COVID-19

**IMMUNOMODULATORS** – severe COVID-19 has been associated with cytokine storm or a cytokine release syndrome (CRS)-like pathology which manifests as rapid clinical deterioration and increased levels of CRP, ferritin, d-dimer, LDH and IL-6 along with fever and ARDS. Degree of CRS related to disease severity possibly mediated by fulminant immune response.

- **IL-6 Inhibitors** High IL-6 associated with increased risk of ARDS and mortality in Wuhan with a suggestion of <sup>56,57</sup> A similar syndrome of CRS seen with CAR T-cell therapy in oncology has been successfully treated with tocilizumab and it holds an FDA indication for CRS associated with CAR T-cell therapy.<sup>42</sup> The IL-6 inhibitors are anti-IL-6 monoclonal antibodies that bind to IL-6, with an intent to mitigate the ongoing immune response in CRS.
  - IL-6 inhibitors currently being investigated in randomized controlled trials
  - Patients with low platelets or neutrophil counts, elevated AST/ALT, or active infections are generally excluded from ongoing clinical trials.
  - Most current data are small, single center case series without a control arm, making it difficult to draw conclusions regarding the impact and potential efficacy on clinical outcomes. Ongoing clinical trials should be forthcoming, but for now this data is extremely preliminary and must be considered in the context of potential risks vs. benefits.

- The NIH/DHHS guidelines say there is insufficient evidence to recommend for or against these agents at this time.
- **Tocilizumab (TOCI)<sup>35</sup>**
  - **Data to support tocilizumab are primarily case reports or small, single-center, open-label case series of tocilizumab without a control group, using inflammatory markers (e.g. CRP) as the primary endpoints along with clinical descriptive endpoints.**<sup>43-46</sup>
    - Most studies included patients with severe COVID-19 infection, and evidence of hyperinflammation through laboratory markers (CRP, ferritin, IL-6, LDH) as per local or regional protocols. Patients were generally given 1-2 doses over 1-3 days. In all of these series, some markers, especially fever and CRP, decline rapidly after infusion (within 7 days) often as part of institutional protocol.
    - In nearly all series patients were also on several other COVID-19 therapies (HCQ or CQ, lop/rit, corticosteroids). Clinical endpoints are difficult to interpret without a control group.
      - One small series from France of matched 30 patients who received tocilizumab to 29 control patients (by age, gender and disease severity using inverse probability of treatment weighted methodology) and found tocilizumab reduced subsequent requirement for mechanical ventilation but did not impact mortality in the weighted population.<sup>36</sup> Unfortunately, the populations were not well matched at baseline, and unclear how well the IPTW accounted for differences in patient population.
      - Press release from Roche released top-line results from CORIMUNO-TOCI trial, where 129 patients with moderate or severe COVID-19 were randomized – 65 to standard care + tocilizumab and 64 to standard care alone, and a significantly lower proportion of patients in the tocilizumab arm met the composite endpoint (need for invasive or non-invasive ventilation or death at day 14) but full results are not available.<sup>23</sup>
    - **Safety:** with long-term use of IL-6 inhibitors for rheumatoid arthritis, an increased risk of severe and opportunistic infections, neutropenia, thrombocytopenia, elevated transaminases and rare gastrointestinal perforation are described. Unclear what risk short treatment course in a different population would entail, and adverse events difficult to interpret in absence of control group.
      - **Adverse events in case series of tocilizumab for COVID-19** reported in 0-92% of patients.<sup>23,43-46</sup> Reported adverse events include hepatic cytolysis and ventilator associated pneumonia in one series, hypertriglyceridemia and pancreatitis, reactivation of herpes simplex and *Candida* isolation from respiratory tract, anemia, QT prolongation, and acute kidney injury, although given the lack of a control group, degree of illness of the patients, and numerous other therapies received, attribution to tocilizumab is not clear.<sup>23,57</sup>
- **Sarilumab (SARI)**
  - **Currently no published data to support sarilumab as treatment for COVID-19 associated CRS.**
  - A press release from Regeneron on 4/27/20 provided an update on the ongoing Phase 2/3 adaptive trial in hospitalized patients. This trial was comparing high dose sarilumab (400mg), low dose sarilumab (200mg) and placebo as an **INTRAVENOUS** single infusion, in two groups of patients – those with severe illness and those with critical illness. An analysis of the Phase 2 randomized data showed rapid reductions in CRP in all treatment arms, but in exploratory clinical outcomes, **no notable benefit was seen in the combined groups**. When separated, there were negative trends for most outcomes in the severe illness group and positive trends in the critical illness group. As a result of this, the severe illness arm was dropped from the Phase 3 trial and only patients who are critically ill will be continued.
    - When discontinued, patients from the severe arm of the phase 3 study were examined, and the trends did not appear to be seen.
- **Siltuximab (SILTUX)**
  - IL-6 inhibitor indicated for treatment of multicentric Castleman's disease

- Small case series of 21 patients from Italy with ARDS on noninvasive mechanical ventilation or CPAP (with elevated CRP and IL-6 levels) described as a preprint – 11 mg/kg IV as a single infusion (5/21 received 2<sup>nd</sup> dose for inadequate response).<sup>37</sup> No control group was available.
  - CRP normalized by day 5 and remained stable in all 16 patients with available data. Clinical improvement noted in 33% (no longer requiring CPAP or NIVV) -worsening in 24%, 1 intubation and one cerebrovascular accident. No other clinical or laboratory data available
- **IL-1 inhibitor: Anakinra**
  - Anakinra inhibits IL-1 activity by competitively binding to IL-1 receptor used to treat auto-inflammatory disorders (e.g. familial Mediterranean fever)
  - IL-1 produced in high levels by macrophages during hyper-inflammation and inhibition of IL-1 activity postulated to also potentially have benefit in treating patients with CRS associated with COVID-19.
  - Current data limited to case reports and small case series but several studies ongoing
    - One retrospective case series from Italy included patients with COVID-19 and ARDS managed outside ICU on non-invasive ventilation (all also received HCQ and lop/rit).<sup>38</sup> Most patients (n=29) received high-dose intravenous anakinra (5 mg/kg IV twice daily over 1 hour) for at least 2 days or until a 75% reduction in CRP and improved respiratory function or until side effects arose, followed by low-dose subcutaneous (SQ) administration if improved. A small number received ONLY low-dose 100 mg SQ twice daily (n=7). A comparison group was patients admitted prior to study initiation who would have met criteria for anakinra (n=16). Groups were fairly well matched other than slightly higher CRP and ferritin in the comparator group, and more patients with severe ARDS in the high-dose anakinra group (no statistics given re: comparison)
    - By Day 21 – 45% of high-dose anakinra patients had been discharged vs. 44% with standard therapy. Mechanical ventilation at day 21 was seen in 17% of anakinra vs. 6% of comparator and death occurred in 10% vs. 44% (p=0.009). Given the small numbers and lack of statistical adjustment for confounders, this study should be confirmed by larger trials
    - **Safety:** treatment was discontinued for adverse events in 24% of patients after a median of 9 days – 14% due to bacteremia and 10% due to increases in serum liver enzymes (although similar outcomes occurred in the comparator group as well)
- **JAK/NAK inhibitors baricitinib, ruxolitinib, tofacitanib**<sup>39</sup>
  - Numb associated kinase (NAK) inhibitor suggested in AI modeling as possible therapy but data limited to case series and further studies ongoing
  - Recent NIH sponsored ACTT trial adapted to change placebo arm to combination of remdesivir + baricitinib (vs. remdesivir alone)
- **Eculizumab**
  - Human monoclonal antibody that binds complement protein C5 and inhibits complement activation
  - Ongoing expanded access study for severe COVID-19
  - Very small case series from Italy – in patients with severe COVID-19 requiring hospitalization, bilateral pneumonia on imaging, requiring oxygen supplementation.<sup>40</sup> Patients received 900mg IV over 35 minutes weekly for up to 4 weekly doses. All received LMWH, lop/rit, HCQ, **ceftriaxone 2g IV daily**, ascorbic acid 6 grams/ day for 4 days, CPAP. Four patients (2 males, 2 females) aged 53-82 admitted to sub-ICU with illness duration 13-18 days, and elevated PT, d-dimer, CRP. All received a total of 2 doses, with rapid decline in CRP (by 48 hrs in all patients). Improvement in chest CT findings was also described and duration of illness ranging from 13-18 days. No mention made of vaccination against meningococcus, and although all patients received ceftriaxone, no specific mention of prophylaxis during therapy
  - **Safety:** eculizumab associated with **severe meningococcal infections** requiring vaccination and prophylaxis

- **Corticosteroids**
  - CDC, SCCM, Surviving sepsis campaign and WHO do NOT recommend corticosteroids routinely unless another indication for use exists
  - VHA Rapid response ESP report systematically evaluated data on corticosteroids
- **Drugs hypothesized to cause harm in patients with COVID-19 and available data to support / refute**
  - **Nonsteroidal anti-inflammatory agents (NSAIDs)**
    - French minister of health, Oliver Veran recommended avoiding NSAIDs and using paracetamol (acetaminophen) for fever after an infectious diseases physician in France cited 4 cases of young healthy patients who developed severe COVID-19 after using NSAIDs in the early stages of disease
    - Editorial published in BMJ laid out a case for possible harm based on observational studies in respiratory tract infections finding NSAIDs associated with increased risk for complications<sup>41</sup>
    - Others have rebutted this as likely confounded by indication and disease severity<sup>42</sup>
    - **Currently the CDC, the European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA) all state there currently is no data to support that NSAIDs are associated with worse clinical outcomes in COVID-19, although the FDA and EMA continue to monitor the situation<sup>43,44</sup>**
  - **Angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) or other renin angiotensin aldosterone antagonists (RAAS)**
    - Hypotheses both of possible benefit and of harm with renin angiotensin blockers (ACE/ARB) and studies are ongoing both to assess impact of these drugs in patients with COVID-19 who are on the medications for another indication. In addition, clinical trials of ACE inhibitors and ARBs as a therapeutic intervention in COVID-19 are registered in Clinicaltrials.gov
    - **The American College of Cardiology, American Heart Association and Heart Failure Association of America released a joint statement on 3/17/20 stating there was no data to demonstrate either a beneficial or adverse outcome with the use of ACE inhibitors, ARBs or other RAAS antagonists in COVID-19 patients and recommended continuation of therapy in those patients who were prescribed these drugs for indications where they are known to be beneficial, such as heart failure, hypertension and ischemic heart disease. They also recommended these drugs not be added beyond standard indications.<sup>45</sup>**
      - A recent meta-analysis of 14 articles involving more than 19,000 patients with COVID-19 did not find use of ACEI or ARBs was associated with a higher risk of COVID-19 infection (OR 0.99; 95% CI 0.95, 1.04), higher severity of infection (OR 0.98; 95% CI 0.87, 1.09) or mortality (OR 0.73; 95% CI 0.5, 1.07) vs. those not taking an ACEI or ARB prior to COVID-19 infection. In contrast, for those patients on antihypertensive medication prior to COVID-19, those with ACEI/ARB exposure had a lower risk of mortality, than non-ACEI/ARB antihypertensives (OR 0.48; 95% CI 0.29, 0.81) p=0.006<sup>46</sup>

See Tables 1-3 for additional information on primary potential therapies for COVID-19 Appendix 1 has information related to additional agents currently being investigated but with no clinical data. Updated information about COVID-19 from the Centers for Diseases Control and Prevention and World Health Organization can be found at:

- [CDC Information for Healthcare Providers on COVID-19](#)
- [World Health Organization Information on COVID-19](#)
- [WHO Compendium of all literature related to COVID-2019](#)
- [NIH/DHHS COVID-19 Treatment Guidelines](#)

Other useful sites of information include

[Association of Health-systems Pharmacists Assessment of evidence for COVID-19 Treatments:](#)



Table 1: Data on Off-label Pharmacotherapeutics studied for potential activity vs. COVID-19

Medication	Study Design	Demographics/results	Outcomes/Comments																																																
<b>Remdesivir (GS-5734)</b> – investigational antiviral with activity against a broad range of coronaviruses. Functions as a nucleotide analog, resulting in viral chain termination. <b>Has completed phase 1 trials (Safety, tolerability and pharmacokinetics) as well as data from compassionate use for Ebola virus infections in 2014</b> <i>Additional ongoing trials in China and other countries</i>																																																			
<b>Wang et al.<sup>10</sup></b>  <b>Remdesivir in adults with severe COVID-19: randomized, double-blind study in China</b>	Investigator-initiated, randomized placebo-controlled, trial of intravenous remdesivir in Wuhan (2:1 randomization) <b>Inclusion:</b> Adults PCR positive for COVID-19 Pneumonia on chest imaging O2 saturation $\leq$ 94% on room air or PaO <sub>2</sub> $\leq$ 300 mmHg <b>Exclusion:</b> Pregnancy/lactation Cirrhosis or AST/ALT > 5 X ULN eGFR < 30 mL/min/1.73 m <sup>2</sup>  <b>Dose:</b> 200mg IV on day 1 then 100mg IV on days 2-10 or placebo  <b>Primary endpoint:</b> Time to clinical improvement within 28 days after randomization (2 point reduction on 6 point ordinal scale or live discharge <i>with NEWS 1 being discharged from hospital not requiring oxygen to NEWS 6 death</i> )	<b>ITT population:</b> planned to enroll 453 patients but due to decreasing cases in Wuhan, study was stopped for difficulty to enroll further  <table border="1"> <thead> <tr> <th></th> <th>Remdesivir n=158</th> <th>Placebo n=78</th> </tr> </thead> <tbody> <tr> <td><b>Age</b></td> <td>66 yrs</td> <td>64 yrs</td> </tr> <tr> <td><b>% male</b></td> <td>56%</td> <td>65%</td> </tr> <tr> <td><b>Hypertension</b></td> <td>46%</td> <td>38%</td> </tr> <tr> <td><b>Diabetes</b></td> <td>25%</td> <td>21%</td> </tr> <tr> <td><b>Coronary disease</b></td> <td>9%</td> <td>3%</td> </tr> <tr> <td><b>Lymphocytes &lt;1</b></td> <td>68%</td> <td>71%</td> </tr> <tr> <td><b>NEWS 3</b></td> <td>82%</td> <td>83%</td> </tr> <tr> <td><b>NEWS 4</b></td> <td>18%</td> <td>12%</td> </tr> <tr> <td><b>Time from symptoms</b></td> <td>11 days</td> <td>10 days</td> </tr> <tr> <td><b>IFN <math>\alpha</math>-2b</b></td> <td>29%</td> <td>38%</td> </tr> <tr> <td><b>Lopinavir/rit</b></td> <td>28%</td> <td>29%</td> </tr> <tr> <td><b>Vasopressors</b></td> <td>16%</td> <td>17%</td> </tr> <tr> <td><b>Corticosteroids</b></td> <td>65%</td> <td>68%</td> </tr> <tr> <td><b>Non-inv. Ventilation</b></td> <td>9%</td> <td>4%</td> </tr> <tr> <td><b>Invasive ventilation</b></td> <td>7%</td> <td>13%</td> </tr> </tbody> </table>		Remdesivir n=158	Placebo n=78	<b>Age</b>	66 yrs	64 yrs	<b>% male</b>	56%	65%	<b>Hypertension</b>	46%	38%	<b>Diabetes</b>	25%	21%	<b>Coronary disease</b>	9%	3%	<b>Lymphocytes &lt;1</b>	68%	71%	<b>NEWS 3</b>	82%	83%	<b>NEWS 4</b>	18%	12%	<b>Time from symptoms</b>	11 days	10 days	<b>IFN <math>\alpha</math>-2b</b>	29%	38%	<b>Lopinavir/rit</b>	28%	29%	<b>Vasopressors</b>	16%	17%	<b>Corticosteroids</b>	65%	68%	<b>Non-inv. Ventilation</b>	9%	4%	<b>Invasive ventilation</b>	7%	13%	<b>Results:</b> <b>Primary outcome: Time to clinical improvement</b> Remdesivir: 21 days Placebo: 23 days Difference 1.23 (95% CI 0.87 to 1.75)  <b>Secondary outcomes:</b> <b>28 day mortality</b> Remdesivir: 14% Placebo: 13% Difference 1.1% (95% CI -8.1% to 10.3%)  <i>If given EARLY (within 10 days of symptom onset)</i> <i>Mortality was 11% vs. 15% (Rem vs. placebo)</i> <i>If given LATE – mortality was 14% vs. 10%</i>  Duration of mechanical ventilation Remdesivir 7 days Placebo 15.5 days Diff -4.0 (95% CI -14.0 to 2.0)  Duration of oxygen support – 19 vs. 21 days Duration of hospital stay – 25 vs. 24 days
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<b>Beigel et al.<sup>11</sup></b>  <b>Remdesivir vs. placebo for patients with severe COVID-19</b>	NIAID sponsored randomized, placebo-controlled trial of hospitalized patients with COVID-19 and one of the following 1. Radiographic evidence 2. Oxygen sat $\leq$ 94% on room air OR 3. Requiring supplemental oxygen, or mechanical ventilation  Dose 200mg x 1, followed by 100mg daily for 9 days Patients with eGFR < 30 mL/min, pregnancy or severe elevation AST/ALT excluded	<b>Study cohort included 541 patients randomized to remdesivir and 522 to placebo</b>  <b>Demographics:</b> Mean age 59 yrs in both groups 65% and 64% were male 53% remdesivir and 52% placebo pts had 2 or more comorbid conditions  Severity of illness (remdesivir vs. placebo) 4 (hospitalized, not requiring oxygen) 12.4% vs. 11.5% 5 (hospitalized, requiring oxygen): 41% vs. 38%	<b>Results:</b>  Median time to recover was 11 days with remdesivir vs. 15 days with placebo with rate ratio for recovery 1.32 (95% CI 1.12-1.55), p<0.001  Mortality at 14 days: 7.1% remdesivir vs. 11.9% placebo (HR death 0.70, 95% CI 0.47 to 1.04)  Benefit was primarily significant in patients hospitalized and requiring supplemental oxygen																																																

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

	Primary outcome: Time to clinical recovery (TTCR) based on 7 point ordinal scale	6 (hospitalized requiring noninvasive ventilation or high flow nasal oxygen (18% vs. 19%) 7 (mechanical ventilation/ECMO) 23% vs. 28%	Patients who were on mechanical ventilation nor ECMO did not appear to have benefit, although these are subgroup analyses and should be hypothesis generating  Adverse events were similar between remdesivir and placebo groups
<b>Goldman et al.</b> <sup>12</sup>  <b>Remdesivir 5 vs. 10 days in severe COVID-19 (SIMPLE)</b>	Phase 3, open-label trial in hospitalized patients with severe COVID-19 randomized to 5 or 10 days of remdesivir. Inclusion: hospitalized with COVID-19 and 1. Radiographic evidence OR 2. Oxygen sat ≤ 94% on room air OR 3. Requiring supplemental oxygen <i>Patients on mechanical ventilation or ECMO, those with eGFR &lt; 50 mL/min, or AST/ALT &gt; 5 times normal were excluded</i>  Dose 200mg x 1, followed by 100mg daily for 4 or 9 days  Initial primary outcome: proportion of patients with normalization of fever and oxygen saturation by day 14, but changed to 7 point ordinal scale as above Safety outcome included adverse events	<b>Demographics (5 vs. 10 days, respectively)</b> Median age 61 vs. 62 yrs. Male sex: 60% vs. 68% Caucasian: 71% vs. 70% HTN 50% of each group, DM 24% and 22%  Initial clinical score 3 (noninvasive ventilation/high flow nasal oxygen): 24% vs. 30% 4 (low flow supplemental oxygen): 56% vs. 54% 5 (not on supplemental oxygen): 17% vs. 11%  Median duration of symptoms was 8 days in the 5 day and 9 days in the 10 day groups	<b>Outcomes:</b> Clinical status at day 14, 5 day vs. 10 days, respectively 1 (Death): 8% vs. 11% 2 (mechanical ventilation): 8% vs. 17% 3 (noninvasive ventilation): 4% vs. 5% 4 (low flow oxygen): 10% vs. 7% 5 (no oxygen but other ongoing care): 6% vs. 7% 6 (hospitalized but no oxygen or ongoing care): 4% vs. 2% <b>7 (Not hospitalized): 60% vs 52%</b>  Median time to clinical improvement was 10 days vs. 11 days  Adverse events in 70% of the 5 days group vs. 75% of the 10 day group – difficult to assess in absence of control group.
<b>Chloroquine (CQ) / Hydroxychloroquine(HCQ)</b> –antiviral agent with activity vs. several viruses, including coronaviruses, thought due to ability to create an alkaline environment which hampers pH dependent viral replication			
<b>Geleris et al.</b> <sup>21</sup>  Observational study of HCQ in hospitalized patients with COVID	<b>Observational study of patients hospitalized with COVID at a large hospital in New York</b>  Patients were classified as receiving HCQ if given at baseline (24 hrs after arrival at emergency department) or during follow-up (but before intubation or death)  Other variables obtained from data warehouse and Cox proportional-hazards regressions models used to estimate association between HCQ and composite primary endpoint (Need for intubation or death). Propensity score methods used to reduce confounding and primary	<b>Identified 811 HCQ and 565 NO-HCQ in the unmatched cohort and were able to identify 274 propensity matched patients</b>  Baseline characteristics in matched cohort similar, including age, comorbidities and vital signs More HCQ patients received azithromycin, other antibiotics, tocilizumab Ferritin, LDH, CRP slightly higher in HCQ group	<b>Outcomes:</b> <b>Overall events:</b> HCQ: 262/811 (32.3%) No-HCQ: 84/565 (14.9%) HR 2.37 (95% CI 1.84 to 3.02) <b>MV analysis</b> HR 1.00 (95% CI 0.76 to 1.32) <b>Propensity score analyses</b> With IPTW: aHR 1.04 With matching: aHR 0.98 Adjusted for propensity score 0.97  <i>Additional support of lack of large benefit of HCQ in hospitalized patients, but given observational nature and</i>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

	analysis used inverse probability treatment weighting (IPTW)		<i>initial mismatching of groups, possibility of residual confounding exists</i>
<p><b>Magagnoli J. et al.<sup>20</sup></b></p> <p>Outcomes of hydroxychloroquine usage in United States Veterans hospitalized with COVID</p>	<p><b>Multicenter, retrospective analysis of patients in VHA hospitals with COVID-19 who received HCQ, HCQ + azithromycin or standard care only</b></p> <p>Primary outcomes: death or need for mechanical ventilation</p> <p>Association between treatment and outcome done using propensity score to adjust for clinical characteristics</p> <p>Medication exposure classified if documented as given during hospitalization (BCMA) but dose and duration not described</p> <p>No evaluation of adverse events</p>	<p><b>Identified 385 hospitalized Veterans who met criteria but excluded the 17 female Veterans - final analysis cohort was 368 adult male patients:</b> 97 HCQ, 113 HCQ+azithro, 158 Std care</p> <p>Were significant differences in baseline characteristics of baseline oxygen saturation, systolic BP, ALT/AST, albumin, bilirubin, WBC, lymphocytes, hematocrit, platelets, CRP, troponin I (baseline characteristics after propensity matching not available)</p>	<p><b>Outcomes:</b></p> <p><b>Deaths:</b> HCQ 27.8%, HCQ+ azithro: 22.1%, Std care: 11.4%</p> <p><b>Need for mechanical ventilation:</b> HCQ 13.3%, HCQ+azithro 6.9%, Std care 14.1%</p> <p><b>Adjusted analysis of propensity matched groups</b></p> <p><b>Death</b></p> <p>HCQ vs. no-HCQ: <b>aHR 2.61, (95% CI 1.1 to 6.17)</b></p> <p>HCQ + azithro vs. no-HCQ: aHR 1.14 (95% CI 0.56 to 2.32)</p> <p><b>Need for mechanical ventilation</b></p> <p>HCQ vs. non-HCQ: aHR 1.43 (95% CI 0.53 to 3.79)</p> <p>HCQ+azithro vs. no-HCQ 0.43 (95% CI 0.16 to 1.12)</p>
<p><b>Mahevas et al.<sup>19</sup></b></p> <p>Clinical efficacy of HCQ in patients with COVID-19 pneumonia who require oxygen: observational comparative study using routine care data</p>	<p><b>Multi-center retrospective trial in 4 French hospitals -patients who received HCQ within 48 hours of admission vs. those who did not</b></p> <p>Hospitalized adults without contraindications not treated with another therapy for COVID-19 and not admitted to ICU or with ARDS</p> <p>Dose 600mg daily</p> <p>Primary outcome composite of transfer to ICU within 7 days and/or death</p> <p>All patients had QT measured at baseline and 3-5 days later</p>	<p><b>181 patients included – 84 received HCQ within 48 hrs of admission, 97 did not (8 did receive it later on) and made up the control group</b></p> <p>Median age: 59 yrs HCQ vs. 62 yrs control</p> <p>Male sex: 78% HCQ vs. 65% control</p> <p>All comorbidities less frequent in HCQ group but other than HTN (45% HCQ and 58% control) were infrequent</p> <p>Median time from symptom onset to admission was 7 days.</p>	<p><b>Outcomes:</b></p> <p><b>In IPTW analyses</b></p> <p>Primary outcome: 21% HCQ vs. 22% control (RR 0.93, 95% CI 0.48, 1.81)</p> <p>Results of sensitivity analyses similar to primary</p> <p>Evaluation of less severely ill subgroup (qSOFA &lt; 2) also did not show benefit of HCQ on any outcome vs. control</p> <p><b>Safety:</b></p> <p><b>8/84 (10%) patients experienced EKG changes requiring HCQ discontinuation</b> at median 4 days</p> <p>7 had QTc increase &gt; 60 msec and one patient had QTc &gt; 500 msec 1 episode of left bundle branch block in a patient who received HCQ and lopinavir/ritonavir later</p>
<p><b>Rosenberg et al.<sup>22</sup></b></p>	<p><b>Retrospective study from random sample of patients at multiple hospitals in NYC, categorized into treatment groups based on exposure to HCQ, azithro, HCQ+azithro or neither</b></p> <p>Primary outcome in-hospital mortality with additional secondary outcomes cardiac arrest and EKG findings (arrhythmia or prolonged QT)</p>	<p><b>Ultimately included 1438 patients</b></p> <p><b>735 HCQ + azithro</b></p> <p><b>271 HCQ</b></p> <p><b>211 azithro</b></p> <p><b>221 neither drug</b></p> <p>HCQ initiated mean 1 day after admission (azithro median 0 days)</p> <p>Median age similar among groups (61.4-65.5 years)</p> <p>Combo group more likely to have low O2 saturation, abnormal chest imaging, elevated AST/ALT</p>	<p><b>Outcomes:</b></p> <p><b>On unadjusted analyses, patients receiving HCQ, or HCQ + azithromycin had higher rates of ICU entry, need for mechanical ventilation or death</b></p> <p><b>Adjusted analyses: In-hospital death (each vs. no drug)</b></p> <p>HCQ+ azithro: aHR 1.35 (95% CI 0.75 to 2.4)</p> <p>HCQ: aHR 1.08 (95% CI 0.63 to 1.85)</p> <p>Azithro: aHR 0.56 (95% CI 0.26 to 1.21)</p> <p><b>Cardiac arrest:</b></p> <p><b>HCQ + azithro: aHR 2.13 (95% CI 1.12 to 4.05)</b></p> <p>HCQ: aHR 1.91 (95% CI 0.96 to 3.81)</p> <p>Azithro: aHR 0.64 (95% CI 0.27 to 1.56)</p>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

	Cox proportional hazards model fit for time to death – controlling for treatment group and potential confounders		<b>HCQ vs. azithro aHR 2.97 (95% CI 1.56 to 5.64)</b> <b>Abnormal EKG:</b> HCQ + azithro: aHR 1.55 (95% CI 0.89 to 2.67) HCQ: aHR 1.50 (95% CI 0.88 to 2.58) Azithro: aHR 0.95 (95% CI 0.47 to 1.94) Adverse events more common in groups receiving HCQ, including diarrhea, abnormal EKG, arrhythmia
<b>Tang et al.<sup>16</sup></b>  Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial	<b>Multi-center, open-label, centrally randomized controlled trial of HCQ + standard of care or standard of care alone in hospitalized patients with COVID-19 in China</b>  Enrolled adults without contraindication to HCG hospitalized with mild/moderate or severe COVID-19 (stratified by severity). Dose was 200mg daily x 3 days, then 800mg daily for 14 days (mild/mod) or 3 weeks (severe)  Primary endpoint % negative viral PCR at day 28 (but viral swabs done at days 4,7,10,14,21 and 28). Secondary outcomes were alleviation of symptoms, labs and radiology day 28	<b>191 patients were screened and 150 were included (41 did not meet eligibility criteria) – 75 in each group</b>  <b>Mean age:</b> 46 years, 55% female Mean time from onset of symptoms was 17 days 60% concomitant medication before randomization <b>99% had mild/moderate disease</b> Pts in HCQ group slightly older (48 vs. 44 yrs), more mild infection (20% vs. 9%) and more co-existing conditions (37% vs. 23%) but similar vital signs, symptoms and laboratory parameters.  Some inflammatory markers slightly higher in the HCQ arm, including CRP (9.9 vs. 7.4) and IL-6 (12.9 vs. 8.9) but consistent with mild/mod disease	<b>Outcomes:</b> At day 28, 85% of HCQ vs 81% of std care patients had negative viral PCR. Negative conversion at specific other time points was similar between groups No difference in time to negative conversion (8 vs. 7 days)  Time to alleviation of symptoms similar (19 vs 21 days)  HCQ did appear to result in more rapid normalization of CRP and lymphopenia  <b>Safety: No mention made of EKG monitoring or cardiac adverse events, but overall adverse events were more common with HCQ (30%) than without (9%), including diarrhea in 10%.</b>
<b>Chen et al.<sup>18</sup></b>  Open label randomized trial of HCQ vs standard care in hospitalized patients with mild COVID pneumonia	<b>Open-label RCT of adults mild COVID-19 (PaO2/FiO2 &gt; 300 mmHg SaO2 &gt; 93%) randomized to HCQ 200mg BID x 5 days + std. care OR Standard care alone (oxygen, antiviral agents, antibacterials and immunoglobulin with or without corticosteroids)</b> <b>Primary endpoint:</b> Differences in time to clinical recovery 5 days after enrollment. TTCR was only assessed in those patients having the symptom at baseline <b>Secondary:</b> progression to severe illness, radiographic improvement day 0 to 6 chest CT	<b>Demographics:</b> 62 patients were enrolled and all completed study  Mean age 45 years (44 yr HCQ vs 45 yr std) 47% male (48% vs. 45%) At baseline fever: 71% HCQ vs. 55% of std care At baseline cough: 71% HCQ vs. 48% of std care <b>No other demographics or baseline characteristics provided to identify relative similarity in severity of illness, comorbidities or risk for poor outcomes</b>	<b>Results:</b> <b>TTCR Fever:</b> 2.2 d HCQ vs. 3.2 d std.(p=0.0008) <b>TTCR cough:</b> 2.0 d HCQ vs. 3.1 d std. (p=0.0016)  Progression to severe illness in 4 of 62 patients in std. treatment arm (6.5%) vs. none in HCQ arm (not defined)  <b>Overall chest CT improved:</b> 81% HCQ vs. 55% std. care <b>Safety:</b> Two patients on HCQ developed mild adverse reactions – one rash and one headache
<b>Gautret et al.<sup>15</sup></b>  Cohort study Marseille, France of patients who received hydroxychloroquine vs. untreated patients and viral load	<b>Open-label cohort of 20 hospitalized patients with COVID-19 who received hydroxychloroquine 200mg three times daily vs. 16 control patients</b>  Of note – patients were excluded if allergy to chloroquine or hydroxychloroquine, G6PD deficiency, AQ prolongation, retinopathy, pregnancy or breastfeeding	<b>Demographics:</b> Mean age 47 years – HCQ pts older (51 vs. 37 yrs) 17% asymptomatic  <b>Six of HCQ pts also received azithromycin (500mg x 1, then 250mg daily for 4 days) to prevent bacterial infection with DAILY EKG</b>  <b>Mean HCQ conc. 0.46 ug/mL</b>	<b>Proportion with negative PCR (HCQ vs. control)</b> <b>Day 6:</b> 70% vs. 13% <b>% with negative PCR (HCQ+azithro vs. HCQ mono)</b> <b>Day 6:</b> 100% vs. 57% <b>Limitations:</b> <b>SIX patients</b> in HCQ arm were not included in analysis – of those 3 transferred to the ICU, one died, and one dc'd due to adverse event – NOT counted as failures

			<p>-patients in control group often did not have daily PCR levels (vs. all of the HCQ arm) and 44% were not tested on at least 4 of 7 visits</p> <p>- All patients with HCQ+azithro had low levels of virus (Ct&gt; 22 on PCR). Of 5 patients with HCQ and Ct &lt;22 or less, 4/5 were detectable on day 6 (similar to control)</p>
<p><b>Huang et al.<sup>17</sup></b></p> <p>22 patients in China randomized to Lop/rit or CQ</p>	<p><b>RCT in China – 82 patients screened, 22 included</b> (criteria unclear but appeared excluded primarily due to contraindications to medications)</p> <p>randomized to CQ 500mg BID or Lop/rit 400/100 BID x 10days</p>	<p><b>Demographics:</b> <b>CQ:</b> 3 severe, 7 moderate cases, median age 42 yrs, time from onset to treatment = 2.5 days, vital signs between groups similar but labs CD4 582, 80% had ground-glass opacities on CT</p> <p><b>Lop/rit:</b> 5 severe, moderate cases, median age 53 yrs Time from onset to treatment = 6.5 days CD4 413, 83% had ground-glass opacities on CT</p>	<p><b>Outcomes:</b> <b>RT PCR time to negative similar – 100% at day 14 for CQ vs. 92% for Lop/rit</b> <b>CT scan improvement at day 14 – 100% CQ vs. 75% lop/rit: Clinical outcomes:</b> hospital discharge by day 14 100% CQ vs. 50% lop/rit</p> <p>Adverse reactions: 90% of CQ pts vs. 83% lop/rit CQ: vomiting and diarrhea 50%, nausea 40%, rash 10%, cough 40% and shortness of breath 10% .GI side effects seen in similar numbers of lop/rit but also neurologic adverse events – dizziness, headache and psychosis</p>
<p><b>Yao et al.<sup>16</sup></b></p> <p>In vitro activity and PK modeling of dosing CQ/HCQ</p>	<p>In vitro activity and pharmacokinetic modeling various dosing regimens for CQ and HCQ for COVID-19</p>	<p><b>In vitro (simulating treatment):</b> CQ EC<sub>50</sub> 24/5.5 uM at 24 hr. and 48 hr. HCQ EC<sub>50</sub> 6/0.7 uM 24 hr. and 48 hr. <b>In vitro when added prior to viral challenge (simulating prophylaxis):</b> CQ EC<sub>50</sub> &gt; 100/18 uM at 24/48 hr.</p>	<p>In vitro activity of HCQ was superior to CQ Using simulated PK models calculated a ratio of free lung trough concentrations to EC<sub>50</sub> to calculate measure of presumed effectiveness R<sub>LTEC</sub> <b>Suggested ideal HCQ dose may be 400mg BID x 1 day, then 200 mg BID on days 2-5 to balance efficacy, safety and compliance</b></p>
<p><b>Protease inhibitors: Lopinavir/ritonavir (Lop/rit), Darunavir + ritonavir or cobicistat (DRV/r, DRV/c)</b>– antiviral agent used in treatment of HIV infection with in vitro activity against several coronaviruses leading to study and use in COVID-19. Lop/rit appears more active in vitro because inhibits COVID-19 protease, but possible that would require higher doses than currently used to be clinically effective and clinical trials are ongoing. Darunavir (with ritonavir or cobicistat) does NOT appear to have activity in vitro or in vivo efficacy</p>			
<p><b>Cao et al.<sup>28</sup></b></p> <p>Randomized trial of lop/rit vs. standard care for severe COVID in China</p>	<p><b>Randomized, open-label trial in patients in patients with severe COVID-19</b> (O<sub>2</sub> sat. ≤ 94% or PaO<sub>2</sub>/FiO<sub>2</sub> ≤ 300 mmHg)</p> <p>Lop/rit. (400mg/100mg) BID (n=99 in ITT but 94 received treatment as assigned) vs. Standard therapy (n=100) For 14 days</p> <p>Primary outcome: time to clinical improvement based on 7 point ordinal scale (1 = resumption of normal activity, 7 = death)</p>	<p><b>Demographics:</b> Median age 58 years with few comorbidities Median 13d from illness onset At baseline – majority were ordinal score 4 (in hospital requiring supplemental oxygen)</p> <p>More patients in std. care arm were on vasopressors, renal replacement, non-invasive or invasive ventilation</p> <p>95% in each arm received antibiotics 32% lop/rit and 35% std. care received glucocorticoids for median of 7 and 6 days, resp.</p>	<p><b>Primary outcome (Time to clinical improvement) 16 days for each group</b></p> <p><b>28 day mortality (ITT)</b> Lop/rit: 19% vs. Std care: 25%. Diff -6% (95% CI -17, 6) Length of ICU stay: 6 days Lop/rit vs. 11 days std care. Difference -5 days (95% CI -9, 0) undetectable viral RNA did not differ between groups at any time point <b>At day 28, only 60% of lop/rit and 59% of std. care were undetectable</b></p> <p>Adverse events 48% of lop/rit and 50% of std. care and grade 3 or 4 AE in 21% lop/rit vs. 11% Std. care Nausea, vomiting, diarrhea more common with lop/rit</p>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

			- <b>Serious AE of respiratory failure/ARDS in 13% lop/rit vs. 27% std. care</b>
<b>Zhu et al.<sup>47</sup></b>  Small retrospective comparison of Lop/rit vs. arbidol in China	<b>Retrospective analysis of Lop/rit 400/100 q12h for 1 week vs. arbidol 0.2g three times daily in hospitalized patients in China</b>  All patients received oxygen and inhaled interferon (IFN- $\alpha$ 2b) 5 million units q12h  Primary outcomes: antiviral effect and safety of lop/rit and arbidol	<b>Demographics: lop/rit n=34, arbidol n=16</b> Median age: Lop rit 41 yrs, arbidol 27 yrs Male sex: Lop/rit 59%, arbidol 38% CRP on admission: Lop/rit 7.7, arbidol 1.1	<b>Results:</b> <b>Day 7 viral load:</b> undetectable 24% lop/rit vs 50% arbidol <b>Day 14:</b> undetectable in 56% lop/rit and 100% arbidol Patients in arbidol arm had shorter duration of positive RNA (p<0.01) 3 patients in each group developed elevated ALT in the first week (<125 U/L) – no other side effects mentioned
<b>IL-6 inhibitors: Tocilizumab(Toci) / Sarilumab(Sari) / Siltuximab (Siltux)</b> – anti-IL-6 biologics used for Rheumatoid arthritis Extremely limited data based on evidence that severe COVID-19 disease is often associated with elevated IL-6, and a syndrome consistent with cytokine release syndrome (CRS). From China, has been shown that elevated IL-6 levels are associated with poor outcomes with COVID-19 <sup>48,49</sup> Added to Chinese guidelines for patients with severe COVID-19 and associated CRS, and is indicated for CRS associated with CAR-T therapy <sup>50</sup> <i>Associated with significant side effects in RA, including <b>serious infections, gastrointestinal perforation</b> and anaphylaxis. In RA patients need to be screened and initiated on therapy for latent or active tuberculosis prior to initiation of therapy</i>			
<b>Xu X, et al.<sup>51</sup></b>  Retrospective review of 21 severe or critical patients who received <b>tocilizumab</b>	<b>Retrospective analysis of 21 patients in China with severe COVID-19 given tocilizumab – no control group</b> Dose: 400mg x 1 but 3/21 received 2 <sup>nd</sup> dose 12 hours later  All patients also were on corticosteroids, inhaled IFN- $\alpha$ , ribavirin, lop/rit, and oxygen	<b>Demographics</b> Mean age 57 years 81% severe, <b>19% critical</b> Comorbidities: DM (43%), HTN (24%), CHF (10%) <b>Only 2 on mechanical ventilation, one on non-invasive ventilation</b> 85% had lymphopenia All had increased CRP and IL-6 levels All had findings on CT scan consistent with COVID worsening in the 7 days prior to toci	<b>Outcomes:</b> By day 5: CRP normal in 84% and lymphocyte count 52%  Temperature normalized by first day after treatment 75% had reduced oxygen by day 5 and ultimately all patients were discharged after mean of 15 days  No serious adverse events noted
<b>Luo P et al.<sup>52</sup></b>  Retrospective case series 15 patients (12 males, 3 females) in Wuhan China of <b>tocilizumab</b>	<b>Retrospective case series of 15 moderately, seriously or critically ill patients in China treated with tocilizumab</b>  Clinical outcomes at 1 week: death, disease aggravated, clinical stabilization or improvement  Widely varying doses from 80mg to 600mg and from 1 to 3 doses 8 patients also received methylprednisolone	<b>Demographics</b> Median age 73 years, 10/15 had comorbidities <b>13% moderately, 40% seriously and 47% critically ill</b> CRP and IL-6 elevated in all	<b>Results:</b> <b>Improvement: 7%, stabilized: 60%, worsened: 33%</b> <b>Clinical status at day 7 was</b> Death: 3/15 (20%) Disease aggravation: 2/15 (13%) Clinical stabilization: 9/15 (60%) Clinical improvement: 1/15 (7%) <b>All deaths occurred in patients categorized as critically ill at baseline</b>
<b>Alattar et al.<sup>53</sup></b>  Open-label, retrospective evaluation of 25 patients with severe COVID-19 in Qatar who received <b>tocilizumab</b>	<b>Retrospective case series of patients requiring ICU care with elevated CRP who received tocilizumab. All also offered supportive antivirals (HCO, azithromycin, lop/rit, ribavirin, interferon)</b> Tocilizumab given IV via protocol (not stated)  Primary outcome – discharge alive from ICU by day 14	<b>Demographics:</b> 25 patients – 92% male Median age 58 years Comorbidities: DM (48%), CKD (16%), CAD (12%) Median Charlson comorbidity score = 1  92% had fever, 84% cough and 72% dyspnea All had pulmonary infiltrates and ground glass opacities (bilateral 92%) - results imply 21 were on invasive ventilation at time of tocilizumab initiation	<b>Primary outcome:</b> <b>36% (9/25) discharged alive from ICU by day 14, 12% died by day 14, 52% still in ICU at day 14</b> Proportion of patients on mechanical ventilation: Day 0: 84%, Day 7: 60%, Day 14: 28% (p=0.001) Temperature and CRP declined steadily over initial 7 days, but no statistically significant increases in lymphocytes

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

	<p>Additional outcomes: Categorical ventilatory status, Inflammatory markers over 14 days, adverse events</p>	<p>Other therapy: (median # antivirals per patient = 5) HCQ: 100%, Azithromycin: 96%, Lop/rit: 96%, Ribavirin: 88%, Interferon 1-<math>\alpha</math>2a: 60% Tocilizumab started within 1 day admission to ICU and patients received median 1 dose of 5.7 mg/kg</p>	<p>92% of patients experienced at least one adverse event – anemia (64%), increased ALT (44%), QT prolonged (20%) <b>Of note – 4 patients developed secondary bacterial respiratory tract infections. <i>Candida spp.</i> isolated from 32% patient in respiratory tract.</b> <b>One patient - reactivation of oral herpes simplex</b></p>
<p><b>Sciascia et al.<sup>54</sup></b>  Peer-reviewed open-label case series of 63 adult patients with severe COVID-19 in Italy who received <b>tocilizumab</b></p>	<p>Included hospitalized patients with a. PCR confirmed COVID-19 b. pulmonary involvement (O<sub>2</sub> sat &lt; 93% on room air or PaO<sub>2</sub>/FiO<sub>2</sub>&lt;300 mmHg) c. Pro-inflammatory/thrombotic profile (varying degrees elevation of at least 3 of CRP, ferritin, d-dimer, LDH)  Dose was 8 mg/kg IV or 325 mg subcutaneous (according to drug availability)  Primary endpoint was <b>drug safety</b> Secondary endpoints were improvement in respiratory and laboratory parameters (patients were followed for at least 14 days <b>after admission</b>)</p>	<p>Overall 63 patients included, 56 male (88%) Mean age 63 years Comorbidities: HTN (38%), DM (10%), CAD (7%) 95% had bilateral infiltrates 8% were on invasive mechanical ventilation  Other therapies Antivirals (100%) – Lop/rit in 71%, Drc/c 29%  Tocilizumab dosing: Intravenous: 54% - and 91% of those received 2<sup>nd</sup> dose Subcutaneous: 46% - 72% of those received 2<sup>nd</sup> dose</p>	<p><b>No patients reported severe to moderate adverse events directly related to tocilizumab (Primary outcome)</b>  <b>Secondary outcomes:</b> Mortality 11% (7/63) and did not differ by route of administration (13% for IV vs. 10% for SQ) – 2 patients remained on mechanical ventilation by day 14 D-dimer, CRP declined significantly by day 1 Change in ferritin and lymphocytes was not significant PaO<sub>2</sub>/FiO<sub>2</sub> increased from admission 152 mmHg to 284 mmHg at day 7 and 302 mmHg by day 14 (p&lt;0.05)  d-dimer at baseline (but not IL-6) predictive of mortality  Use of tocilizumab within 6 days from admission was associated with increased likelihood of survival (HR 2.2, 95% CI 1.3-6.7, p&lt;0.05)</p>
<p><b>Roumier et al.<sup>23</sup></b>  Tocilizumab in 30 selected patients in France, retrospectively compared with matched control group</p>	<p>30 patients treated between 3/21 – 4/2/20 with tocilizumab as compassionate use. Criteria to receive were less than 80 yrs. Old with rapidly deteriorating condition (increase O<sub>2</sub> by <math>\geq</math>3L/min within previous 12 hrs), pneumonia, high CRP levels and within 5 days of disease onset)  Matched with 29 controls (for age, gender and disease severity) using inverse probability treatment weighting to adjust for confounding and develop propensity score  Endpoint not stated in methods but reported on need for mechanical ventilation, mortality, and for those not in ICU – risk of transfer to ICU</p>	<p>Demographics: Weighted pop. – tocilizumab vs. control Age – 62.3 vs. 60.6 yrs Female sex – 22% vs 16% ICU – 33% vs. 50% COPD – 15% vs. 16% DM: 30% vs. 28% NEWS score <math>\geq</math>7: 83% vs. 86% CRP: 187 vs. 161 mg/L  2 tocilizumab patients also received HCQ + azithro and 2 control patients received high dose steroids</p>	<p><b>As of 4/4/20 – Overall mortality 10%, 20% discharged from hospital</b>  After median follow up of 8 days, tocilizumab reduced need for mechanical ventilation (weighted OR 0.42; 95% CI 0.20 to 0.89), p=0.025.  Unadjusted analysis showed trend to reduced mortality but disappeared  Comparing 23 tocilizumab patients to 16 (matched?) control patients not in ICU, tocilizumab decreased risk of ICU admission (weighted OR 0.17; 95% CI 0.06 to 0.48)</p>
<p><b>Capra et al.<sup>55</sup></b>  Retrospective analysis of tocilizumab with</p>	<p><b>Retrospective analysis of 62 patients treated with tocilizumab matched to 23 patients treated with standard care in time prior to tocilizumab availability</b></p>	<p><b>Demographics:</b> Age: Toci 63 years, std care 70 yrs. Male sex: toci 73%, controls 83% HTN (46% vs 48%), CAD (14% vs. 26%)</p>	<p><b>Results:</b> More patients in the tocilizumab arm (60% vs. 17%) did not have a known outcome at time of final observation (enrolled later)</p>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

<p>matched controls in Italy</p>	<p>Generally patients were hospitalized with severe COVID19 but not requiring mechanical ventilation Dose was 400mg IV (53%), 800mg IV (3%) or 324 mg SQ (44%)</p>	<p>All patients also received HCQ 400mg daily and Lop/rit 800/200mg daily</p>	<p>By April 2<sup>nd</sup>, 3% of tocilizumab and 48% of control group died (63% of tocilizumab and 17% of control patients were still undergoing follow up)  <i>Results difficult to interpret in light of high rate of patients still undergoing follow up but encouraging</i></p>
<p><b>Klopfenstein et al.<sup>56</sup></b>  Retrospective analysis of tocilizumab vs. previous patients with standard care only</p>	<p><b>Retrospective case-control study in France of patients who received tocilizumab + std care vs. std care alone</b> (HCQ or lop/rit, oxygen) Patients were hospitalized with evidence of inflammatory markers and respiratory failure without contraindications  Control patients were enrolled from time before tocilizumab was available Primary endpoint: composite of death/ICU admission</p>	<p><b>Demographics:</b> <b>20 toci and 25 std care patients</b> More patients in toci group &gt; 70 years old (75% vs. 44%)  toci patients had higher Charlson comorbidity index (5.3 vs. 3.4)</p>	<p><b>Results:</b> Composite death/ICU admission occurred in 25% tocilizumab vs. 75% standard care patients (p=0.002)  <i>Difficult to assess impact of time bias using previously admitted patients as control group but again encouraging results with tocilizumab</i></p>
<p><b>Colaneri et al.<sup>57</sup></b>  Retrospective analysis of tocilizumab vs. matched controls with standard care</p>	<p><b>Retrospective analysis of hospitalized patients with evidence of hyperinflammation and low oxygenation who received tocilizumab vs. matched control group of patients from time prior to tocilizumab availability who received std care</b> (HCQ, azithromycin, LMWH and methylprednisolone)  Primary outcome: ICU admission and 7 day mortality Secondary outcomes: laboratory measures and adverse events</p>	<p><b>Demographics:</b> <b>21 Toci patients and 91 std care</b>  In entire cohort – 73% male, median age 64 yrs Minimal additional demographics provided</p>	<p><b>Results:</b> After logistic regression analysis, tocilizumab was not associated with likelihood of ICU admission or death vs. standard care</p>
<p><b>Press Release: CORIMUNO-19 PARIS<sup>58</sup></b>  Multi-center, open-label, RCT of <b>Tocilizumab</b> in hospitalized patients with moderate or severe COVID-19 in Paris</p>	<p>One of a series of ongoing RCT in France (CORIMUNO trials) of toci + standard of care (SOC) vs. SOC alone  2 cohorts of patients – one with moderate and another with severe COVID-19 infection  Dose is 8 mg/kg IV with option for 2<sup>nd</sup> dose at day 3  Primary outcome: need for ventilation (invasive or non-invasive) or death at day 14</p>	<p>Randomized 65 patients to tocilizumab + SOC and 64 patients to SOC alone  No other information available at this time regarding demographics, baseline characteristics, similarity between groups</p>	<p><b>In the press release, investigators stated “a significantly lower proportion of patients reached the primary endpoint in the tocilizumab arm”. Results of the study will be submitted for publication in a peer-reviewed journal</b>  Authors stated the results should be confirmed independently by additional trials, but given the pandemic context they felt ethically obligated to disclose the information, pending peer review and while continuing to accrue longer follow-up</p>
<p><b>Press release: REGENERON – Regeneron and Sanofi</b></p>	<p>Press release on 4/27/20 of results after analysis by independent data monitoring committee of all phase 2 and 3 data resulting in an</p>	<p>Phase 2 trial demonstrated sarilumab rapidly lowered CRP, meeting primary endpoint, with no new safety signals</p>	<p><b>Analysis combining severe and critical cases on clinical outcomes identified no notable benefit, but negative</b></p>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

<p>provide update on U.S. Phase 2/3 adaptive designed trial of Kevzara (<b>sarilumab</b>) in hospitalized COVID-19 patients</p>	<p>amendment eliminating the “serious” illness arm and only continuing “critical”</p> <p>Phase 2 portion 457 patients and compared 200mg IV, 400mg IV and placebo (single dose) with either severe illness (28%) or critical illness (49%) or multi-system organ dysfunction (23%)</p> <p>Note – sarilumab was given intravenously in this trial not, subcutaneously as currently FDA approved for rheumatoid arthritis</p>	<p>Analysis of clinical outcomes in the Phase 2 trial was exploratory and pre-specified to focus on the "severe" and "critical" groups and sarilumab had no notable benefit on clinical outcomes when combining the "severe" and "critical" groups, versus placebo.</p> <p>negative trends for most outcomes in the "severe" group, and positive trends in the "critical" group. Subsequent to the IDMC review, Regeneron and Sanofi reviewed the discontinued "severe" group</p>	<p><b>trends in “severe” group and positive trends in “critical” group for all outcomes</b></p> <p>Note that in phase 3 data: negative trends seen in the Phase 2 trial (n=126) were not reproduced in Phase 3 trial (n=276), and clinical outcomes were balanced between sarilumab and placebo, with outcomes that were better than expected based on prior reports</p>
<p><b>Gritti et al.<sup>24</sup></b></p> <p>Case series of 21 patients with COVID-19 in Italy treated with <b>siltuximab</b></p>	<p>Retrospective analysis of 21 patients who received siltuximab 11 mg/kg IV over 1 hour – 2<sup>nd</sup> dose could be given, as part of compassionate use program. All patients were followed up for at least 7 days</p> <p>Patients had confirmed COVID-19 by clinical and radiological assessment and ARDS</p>	<p><b>Demographics:</b>                  Median age: 64 yrs. (range 48-75)                  86% male                  90% had fever, 62% dry cough, 71% dyspnea  <b>Comorbidities:</b> HTN (43%), DM (24%), cardiovascular disease (19%)</p> <p>Baseline CRP elevated in all patients (median 23.4 mg/dL), IL-6 available for 19 patients and was elevated. Median PaO<sub>2</sub>/FiO<sub>2</sub> 127</p> <p>All 21 patients were on CPAP or non-invasive mechanical ventilation</p> <p>5/21 patients received 2<sup>nd</sup> dose</p>	<p><b>Outcomes:</b>                  CRP normalized by day 5 and stable for all 16 patients with available data through follow-up  <b>Improvement 33%, stabilized 43%, worsened 24%</b>                  5/21 required intubation                  7/21 no longer required CPAP/ventilation                  1 patient had cerebrovascular accident</p> <p>No other outcomes reported and no mentioned of adverse events</p> <p>Cohort study of matching patients vs. standard care ongoing.</p>
<p><b>Other immunomodulatory agents: (IL-1 inhibitors, JAK inhibitors, BTK inhibitors):</b> affect immune system at various points with goal to reduce hyperinflammatory state</p>			
<p><b>Cavalli et al.</b></p> <p>Case series with historical control of patients treated with high-dose intravenous anakinra or low dose subcutaneous anakinra (IL-1 inhibitor) vs. standard care alone</p>	<p>Retrospective review of patients who received anakinra for COVID-19 in large hospital in Italy.</p> <p>Criteria for anakinra were COVID-19 with moderate to severe ARDS with hyperinflammation on noninvasive ventilation: Dosing was 5 mg/kg IV over 1 hour twice daily until specific criteria were met (75% reduction in CRP, improved respiratory parameters) followed by SQ anakinra 100mg BID x 3 days</p> <p>Some patients received 100mg SQ BID only</p> <p>Controls were historical patients who received standard care and would have met criteria for</p>	<p><b>Demographics:</b>                  16 control patients were compared with 29 patients who received high-dose IV anakinra, but also included 7 patients who received low dose SQ anakinra</p> <p>Mean age: 70 years in control group, 62 years with high dose anakinra, majority male.</p> <p>Control patients had higher ferritin, CRP</p> <p>Anakinra arm had lower PaO<sub>2</sub>/FiO<sub>2</sub> and more met criteria for severe ARDS</p>	<p><b>Results:</b>                  Anakinra patients had more rapid reduction of CRP</p> <p>Showed overall higher survival at 21 days with anakinra but similar proportion of patients discharged and no difference in mechanical ventilation-free survival</p> <p>Treatment discontinued in 7 patients due to adverse events (24%) after median duration 9 days – 4 cases of bacteremia and 3 increases in liver enzymes</p> <p>Data is hypothesis generating but groups were very small, not well matched and use of historical control may generate bias</p>

	<p>anakinra and also did not receive other immunomodulatory therapy</p>		
<p><b>Interferons (IFN) with or without ribavirin (RBV):</b> note different preparations have been studied with varying degrees of inhibition in vitro vs. human coronaviruses  <b>Note: ongoing trial phase 1 not yet recruiting: <a href="#">NCT04293887</a> of IFN<math>\alpha</math>2<math>\beta</math> on ClinicalTrials.gov</b>  <b>See above study in combination with lopinavir/ritonavir <a href="#">NCT04331899</a> – (COVID-Lambda) - mild COVID-19 treated with PegIFN lambda 1a 180mcg SQ once vs. standard of care looking at duration of viral shedding</b></p>			
<p>Systematic review and meta-analysis of 16 observational studies of treatment for MERS-CoV, including 8 studies of antiviral treatments</p> <p>Included antivirals were IFN-<math>\alpha</math>2a, IFN-<math>\alpha</math>2b, IFN-<math>\beta</math>1a, ribavirin, tenofovir, emtricitabine, lopinavir and ritonavir</p>	<p>IFN treatments included (always in combination with RBV)</p> <ul style="list-style-type: none"> <li>- IFN-<math>\alpha</math>2a (4 studies, 35 pts, dose 180 ug/wk.)</li> <li>- IFN-<math>\alpha</math>2b (5 studies, 22 pts, dose 100-180 ug/wk.)</li> <li>- IFN-<math>\beta</math>1a (2 studies, 12 pts, dose 44 ug/wk.)</li> </ul>	<p>While mortality was reported as 36% for IFN-<math>\beta</math>1b, this was only 11 patients total, limiting ability to make conclusions</p> <p>In comparison of patients treated with IFN vs. supportive care, mortality was 71% with IFN+RBV (n=68) and 71% with supportive care only (n=48) and didn't differ by type</p>	<p>When reported, the delay in therapy from admission to initiation with IFN+RBV was a mean of 12 days</p> <p>Of note, although small – time to initiation in 12 survivors was shorter (1.7 days) vs. those who died (15.1 days)</p>

\*\*\*Note that status of clinical trials is updated from Clinical Trials.gov as of the date in the header  
 +The effective concentration is the concentration of product at which virus replication is inhibited by 50 percent (e.g., EC<sub>50</sub> for cell-based assays). Cytotoxicity tests use a series of increasing concentrations of the antiviral product to determine what concentration results in the death of 50 percent of the host cells ( median cellular cytotoxicity concentration or CC<sub>50</sub>)

Table 2: Selected Characteristics of Potential Therapeutic Agents for COVID-19

DRUG	In vitro activity AND MECHANISM <sup>+</sup>	PHARMACOKINETICS / PHARMACODYNAMICS*	DOSING AND ADMINISTRATION**
<b>Lopinavir/ritonavir</b>	In vitro data vs. many coronaviruses, including SARS and MERS – early data suggested activity vs. COVID-19	PK well described for HIV – ritonavir acts as pharmacokinetic booster to increase levels of lopinavir  Bioavailability requires administration with ritonavir Metabolized by CYP3A4	Should be given with food which could be an issue in hospitalized patients 400/100mg twice daily for 7-14 days has been studied
<b>Chloroquine (CQ)</b>	EC <sub>50</sub> 1.13 uM CC <sub>50</sub> > 100 uM  Thought to exert activity against coronaviruses by concentrating in acidic intracellular organelles such as lysosomes and increasing pH within vesicles and inhibit viral replication. Have also been suggested to play a role preventing viral entry via endosomes  May also function as immunomodulators	Bioavailability 90%  Protein binding 55%  V <sub>d</sub> 200-300 L/kg – extensive tissue distribution to liver, spleen, kidney and lung  C <sub>max</sub> 0.06-0.1 mcg/mL : 300mg single dose  <b>Half-life 10-60 days</b>  Metabolized in liver (2C8, 3A4) – primary metabolite desethylchloroquine 50% excreted unchanged in urine	<i>Note 250mg CQ phosphate = 150mg CQ base (comes as 250mg, 500mg chloroquine phosphate tablets)</i>  Optimal treatment dose unknown: <a href="#">Dose recommendations from FDA Emergency Use Authorization</a> (for adults weighing 50kg or more): <b>1gram CQ phosphate (600mg CQ base) on day one followed by 500mg CQ phosphate (300mg CQ base) daily for total 4-7d</b>  <b>Chinese consensus guidelines recommend 500mg chloroquine phosphate (300mg CQ base) BID x 10 days</b> <i>Daily dose should not exceed 2.3 mg/kg actual body weight</i>  Recently – DMSB stopped high-dose arm (500mg BID) of ongoing RCT in Brazil due to high rate of QT prolongation and 2 cases of torsades de pointes <sup>19</sup>
<b>Hydroxychloroquine</b>	Compared with CQ – HCQ EC <sub>50</sub> was 0.72 uM vs. 5.47 for CQ  Similar proposed mechanisms of activity to CQ vs. COVID-19, although in vitro data suggests increased potency  When given prior to viral challenge: EC <sub>50</sub> 6.25 uM at 24 hr and 5.85 uM at 48 hr	Mean steady state concentration in patients on 400mg daily = 0.42 mcg/mL  Bioavailability variable in rheumatoid arthritis 30-100%  Large volume of distribution  <b>Half-life 40 days</b>  15-30% excreted unchanged in urine  In study by Gautret- mean HCQ concentrations (on 200mg TID) were reported to be 0.46 +/- 0.2 ug/mL  PK study in 13 critically ill patients on 200mg TID for 7 days found only 8/13 achieved a level at least 1 mg/L (at mean of 2.7 days), and 2/13 had concentrations > 2 mg/L. After modeling they	<i>Note: supplied as 200mg tablets – crushing or breaking of tablets not recommended</i>  Optimal treatment dose unknown: Based on modeling and in vitro activity – <b>400mg BID x 1 day, followed by 200 mg BID for 4 days</b>  Other suggested doses: 400mg daily to BID x 5-10 days 200mg TID x 10 days <sup>30</sup>  Compounding suspensions for oral/enteral administration <sup>61</sup>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

		<p>suggested a loading dose of 800mg x 1 followed by 200mg BID would most likely achieve a level of 1-2 mg/L<sup>59</sup></p> <p>Another study in 14 critically ill patients (5 on renal replacement therapy and one on ECMO) noted toxic concentrations in several patients by day 5 of therapy and therapy was stopped or altered in 2 patients, one for prolonged QTc and another for severe hypoglycemia<sup>60</sup></p>	
<b>Remdesivir</b>	<p>Nucleoside analog, broad-spectrum antiviral – inhibits viral replication In vitro EC<sub>50</sub> of 0.77 uM</p>	<p>High first pass effect reduces oral bioavailability</p> <p>Linear PK at doses 3-225mg IV, including with repeated doses of 150mg IV once daily - rapidly distributed to peripheral blood mononuclear cells (PBMCs) w/in 2 hours then activated to nucleoside triphosphate</p> <p>Metabolized to active metabolite <b>GS-443902</b> with prolonged intracellular half-life (&gt;35 hrs) and AUC within mononuclear cells</p>	<p>PK data suggests 30minute infusions may maximize intracellular concentration (vs. 2 hr)</p> <p>Dose in COVID19 Clinical trials and Expanded access = 200mg IV once then 100mg IV daily for 5 or 10 days total</p>
<b>Tocilizumab</b>	<p>IL-6 inhibitor being studied to treated suspected cytokine release syndrome (CRS) with COVID-19 in lungs Holds FDA indication for CRS related to CAR T-cell therapy</p>	<p>Given by intravenous infusion – typically in 100 mL 0.9% or 0.45% sodium chloride over 1 hour Nonlinear elimination (Michaelis-Menten kinetics) – half-life is concentration dependent (ranges 11-19 days) <b>SQ formulation should NOT be given intravenously – NO data on use of SQ tocilizumab for treatment of COVID-19</b></p>	<p>Dose given was 400mg IV x 1 over 60 minutes with a minority of patients given a second dose 12 hours after the first</p>
<b>Sarilumab</b>	<p>IL-6 inhibitor FDA indicated for the treatment of rheumatoid arthritis being studied in phase 2/3 trials to reduce cytokine release syndrome (CRS) with COVID-19</p>	<p>Administered SQ – PK based on 150mg and 200mg mult. Dose Tmax reached at 2-4 days Eliminated through linear and non-linear pathways with conc. Dependent t<sub>1/2</sub> (8-10 days) but detectable for 28-43 days</p>	<p>For RA given as a SQ injection every 2 weeks – supplied as prefilled, single dose pens or syringes of 150mg or 200mg</p> <p>Current phase 2/3 study is looking at a single dose of “low dose”, “high dose” or standard care <b>BUT IS BEING GIVEN INTRAVENOUSLY AS A SINGLE DOSE (dose unclear)</b></p>
<b>Siltuximab</b>	<p>IL-6 inhibitor FDA indicated for treatment of multicentric Castleman’s disease Observational case-control study in Italy being done based on compassionate use</p>	<p>Administered IV with Cmax by end of infusion although steady state not reached until the 6<sup>th</sup> infusion</p> <p>Mild-moderate renal or hepatic impairment did not significantly affect PK</p>	<p>Administered as an IV infusion over 1 hour (diluted in 250mL D5W)– data for CRS in COVID unknown, but for FDA indication, dose is 11 mg/kg</p> <p>Supplied as 100mg and 400mg single dose vials</p>

\*PK/PK, dosing, general information from Kucers' the Use of Antibiotics, 7<sup>th</sup> Ed, 2019

\*\*Dosing is taken from tertiary references, published literature and pharmacokinetics and in vitro data but should be discussed with local experts and is not intended to imply a recommendation

+The effective concentration is the concentration of product at which virus replication is inhibited by 50 percent (e.g., EC<sub>50</sub> for cell-based assays). Cytotoxicity tests use a series of increasing concentrations of the antiviral product to determine what concentration results in the death of 50 percent of the host cells (referred to as the median cellular cytotoxicity concentration or CC<sub>50</sub>)

Table 3: Safety and Drug Interactions of Potential Therapeutic Agents for COVID-19

Drug	Common or Serious Adverse Events	Drug Interactions	Comments
Lopinavir/ritonavir	<p><b>GI Symptoms (diarrhea) which appeared to be significant in COVID-19 patients</b></p> <ul style="list-style-type: none"> <li>-pancreatitis</li> <li>-liver enzyme abnormalities</li> </ul>	<p>Substrate and inhibitor of CYP3A4 Inhibits CYP2D6 but less</p> <p>Major interactions</p> <ul style="list-style-type: none"> <li>-anticoagulants</li> <li>-antiarrhythmics</li> <li>-statins</li> <li>-calcium channel blockers</li> <li>-immunosuppressants</li> <li>-PDE5 inhibitors</li> </ul>	<p>All drug interactions should be closely reviewed by a pharmacist prior to initiation and meds adjusted as indicated – Excellent resource is <a href="#">University of Liverpool interaction tracker</a></p> <p>Diarrhea and other gastrointestinal side effects common</p>
Chloroquine <sup>62</sup>	<ul style="list-style-type: none"> <li>-QT prolongation, arrhythmia and conduction abnormalities</li> <li>-Gastrointestinal distress, nausea, diarrhea, abd. Pain</li> <li>-Neurotoxicity and psychiatric effects (agitation, depression, anxiety, psychosis, seizures, extrapyramidal reactions)</li> <li>-Hypoglycemia (with or without antidiabetic drugs)</li> <li>-Hemolytic anemia with G6PD deficiency, leukopenia</li> <li>-Skin reactions: rash/pruritis, Erythema multiforme – may cause exacerbations of psoriasis or porphyria</li> <li>- Symptoms of overdose include hypotension, AV block, arrhythmias, and electrolyte disturbances</li> <li><b>A single 500mg tablet can be fatal to a child</b></li> </ul> <p><b>Study in Brazil comparing high dose (600mg twice daily x 10 days) vs. low dose (450mg twice daily x 1day, then daily for 4 days) as treatment of COVID-19 in hospitalized patients was stopped early, after 81 patients were enrolled.</b> Overall fatality was 27% and mortality by day 13 was higher in the high dose arm than in the low dose arm (39% vs. 15%). QTc &gt; 500 msec occurred more frequently in the high-dose arm (19%) than in low dose arm (11%) and difference was even more marked in patients with confirmed COVID-19 (24% vs. 4%)</p>	<p>Substrate of CYP2C8, 3A4 Inhibits CYP2D6</p> <p>Inhibits CYP2D6 and to lesser degree CYP3A4</p> <p>Increased levels of drugs metabolized by CYP2D6</p> <ul style="list-style-type: none"> <li>-beta-blockers</li> <li>-antipsychotics</li> <li>-antidepressants</li> </ul> <p>Increased levels of digoxin</p> <p>Increased risk of QT prolongation with other medications that prolong QT</p>	<p><b>QT should be monitored prior to initiation and drug avoided if QT &gt; 490 msec.</b> Ideally patients should be on telemetry, and if tele QTc concordant to EKG QTc can use telemetry for further QTc monitoring:</p> <ul style="list-style-type: none"> <li>○ For patients not on telemetry a repeat EKG should be taken after starting CQ and considered daily if risk factors</li> <li>○ Discontinue all other QT prolonging agents, if possible</li> <li>○ <b>If QTc increases by &gt; 50 msec, or absolute QTc &gt; 500 msec, discontinuation should be strongly considered</b></li> <li>○ Of note, other modifiable risk factors (K+, Mg++) should be monitored and controlled for</li> <li>○ <b>Azithromycin may also prolong the QTc and has been shown to increase the risk of sudden cardiac death</b></li> </ul> <p>Review for drug interactions prior to administration Extreme caution or avoid in patients with history of seizures, conduction abnormalities, preexisting anemia, severe liver dysfunction</p> <p><b>G6PD testing prior to initiation</b></p>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

<p><b>Hydroxychloroquine<sup>63</sup></b></p>	<p><b>Generally considered better tolerated than CQ</b>                  - <b>Pruritis</b>, hypersensitivity, may exacerbate psoriasis or porphyria – a case of a severe exacerbation of psoriasis when given for COVID-19 has been reported<sup>64</sup></p> <p>-<b>Can prolong QTc</b>, PR and QRS, which has resulted in fatal arrhythmia: Risk factors include female gender, age ≥ 65 yrs., baseline prolonged QT/QTc, congenital long QT syndrome, family history of sudden cardiac death before age 50, cardiac disease, electrolyte disturbances, bradycardia, acute neurologic events, DM and autonomic neuropathy as well as use with concomitant drugs that can prolong QT – risk is <b>DOSE DEPENDENT</b></p> <p>-<b>Gastrointestinal distress</b>, nausea, diarrhea, abd. Pain                  -<b>Neurotoxicity and psychiatric effects</b> (including suicidal ideation, seizures, extrapyramidal reactions) muscle weakness                  -<b>Hypoglycemia</b> (with or without antidiabetic drugs)                  -Hemolytic anemia with G6PD deficiency (less of concern than with CQ), leukopenia                  - <b>Symptoms of overdose include hypotension, AV block, arrhythmias, seizures and hypokalemia which often occur within 1-3 hours of ingestion<sup>65</sup></b></p>	<p>Substrate of CYP2C8, 3A4                  Inhibits CYP2D6</p> <p>Inhibits CYP2D6 and to lesser degree CYP3A4 (increased level of cyclosporine has been reported)</p> <p>Increased levels of drugs metabolized by CYP2D6                  -beta-blockers                  -antipsychotics                  -antidepressants                  - Increased levels of digoxin                  Antacids may reduce absorption when given simultaneously with HCQ – separate by 4 hours</p> <p>Increased risk of QT prolongation with other medications that prolong QT, including but not limited to (Class 1A, 1C, III antiarrhythmics, certain antidepressants, antipsychotics, fluoroquinolones, macrolides, 5-HT3 receptor antagonists)</p>	<p>Contraindicated in patients with pre-existing retinopathy of the eye</p> <p><b>EKG should be done at BASELINE</b> - QT should be monitored prior to initiation and drug avoided if QT &gt; 490 msec. Ideally patients should be on telemetry, and if tele QTc concordant to EKG QTc can use telemetry for further QTc monitoring:</p> <ul style="list-style-type: none"> <li>○ For patients not on telemetry a repeat EKG should be taken after starting CQ and considered daily if risk factors</li> <li>○ Discontinue all other QT prolonging agents, if possible</li> <li>○ If QTc increases by &gt; 50 msec, or absolute QTc &gt; 500 msec, discontinuation should be strongly considered</li> <li>○ Of note, other modifiable risk factors (K+, Mg++) should be monitored and controlled for</li> <li>○ <b>Azithromycin may also prolong the QTc and has been shown to increase the risk of sudden cardiac death</b></li> </ul> <p>Review for drug interactions prior to administration</p> <p>Glucose should be monitored closely in patients, especially those with DM on insulin or other medications along with HCQ, lower doses may be required                  Extreme caution or avoid in patients with history of seizures, conduction abnormalities, preexisting anemia, liver dysfunction, renal dysfunction</p>
<p><b>Remdesivir</b></p>	<p>Limited safety data in humans                  Preclinical data showed high safety margins of both remdesivir and GS-441524 with &gt; 3.5 fold margins in most toxicity assays- Animal data suggest a low risk for CNS, respiratory or cardiovascular toxicity at human doses</p>	<p>No published data available</p>	<p>In placebo controlled trial in China adverse events occurred in 66% of remdesivir and 64% of placebo patients                  Rash – 7% with remdesivir vs. 3% placebo                  Thrombocytopenia - 10% remdesivir vs. 6% placebo</p> <p>AST elevation – 5% remdesivir vs. 12% placebo</p> <p>Serious adverse events occurred in 18% remdesivir and 26% placebo patients (6% vs. 13% were grade 3)</p>
<p><b>Tocilizumab</b></p>	<p>Increases risk of severe and opportunistic infections when used for rheumatoid arthritis, including active tuberculosis, invasive fungal infections, bacterial, viral and other opportunistic pathogens                  Neutropenia (1.8-3.4%)                  Hypersensitivity, including anaphylaxis (0.1-0.2%)                  Hepatotoxicity                  Rare cases of gastrointestinal perforation</p>	<p>Live vaccines should be avoided with tocilizumab as clinical safety has not been established</p> <p>May result in increased activity of several CYP enzymes (CYP1A2, 2B6, 2C9/19, 2D6, 3A4) due to inhibition IL-6</p>	<p>AST/ALT should be ordered prior to therapy and in RA tocilizumab is recommended to be discontinued if &gt; 5 x upper limit of normal</p> <p>WBC should be done prior to administration and recommendation in RA is to discontinue if the ANC &lt;500</p> <p>Platelet count is recommended prior to initiation and in RA recommendation to discontinue if platelets &lt; 50</p>

6/11/2020 – Literature Summary on investigational and off label therapies for COVID-19

	Increased total cholesterol, triglycerides, LDL and/or HDL	Patients on drugs metabolized through CYP enzymes with narrow therapeutic indices should be monitored	
<b>Sarilumab</b>	<p><b>Black box warning for increased risk of serious risk of serious infections leading to hospitalization and death, including bacterial (especially pneumonia), viral (zoster reactivation), fungal and other opportunistic infections. Cases of tuberculosis have also been reported</b></p> <p>Neutropenia (7-10%), thrombocytopenia Elevation of transaminases Increases in LDL, HDL, triglycerides</p> <p><b>Rare cases of GI perforation – especially with diverticulitis or in patients on concomitant NSAIDs or corticosteroids</b></p> <p>Hypersensitivity reactions (0.3%)</p>	<p>Live vaccines should be avoided during treatment due to increased risk of infection related to immunosuppression caused by sarilumab</p> <p>IL-6 inhibitors may impact CYP450 enzymes – in patients on simvastatin, one week after 200mg SQ sarilumab, simvastatin conc. Decreased by 45%</p> <p>This may result in significant interaction with other drugs metabolized primarily through CYP450 with a narrow therapeutic index</p>	<p>Sarilumab should be AVOIDED in patients with documented or strongly suspected bacteria, fungal, opportunistic or viral infections (other than COVID-19)</p> <p>CBC should be checked prior to administered with sarilumab avoided if ANC &lt; 500 cells/mm<sup>3</sup> or PLT &lt; 50,000 cells/mm<sup>3</sup></p> <p>Transaminases should be monitored and sarilumab generally avoided if AST/ALT &gt; 5 X ULN</p> <p>No data exists on safety in patients with hepatic impairment including patients with positive HBV or HCV serology</p>
<b>Siltuximab</b>	<p><b>Warnings for active severe infections, infusion reactions and GI perforation</b></p> <p>Contraindicated if severe hypersensitivity <b>Should NOT be administered to patients with severe infections until resolved</b></p> <p>Infusion reactions in 5-6% of patients, and 1 case of anaphylaxis in 945 patients Rash/pruritis in 28% vs. 12% with placebo</p>	<p>Live vaccines should be avoided during treatment due to increased risk of infection related to immunosuppression</p> <p>May result in increased activity of CYP enzymes due to inhibition IL-6. Patients on drugs metabolized through CYP enzymes with narrow therapeutic indices should be monitored</p>	<p>Infusion should be stopped if signs of anaphylaxis</p> <p>For mild to moderate infusion reactions, if the reaction resolves, it can be restarted at a lower infusion rate (consider premedication with antihistamines, acetaminophen)</p>

## Appendix 1: Investigational Therapeutic Agents under evaluation as Possible Treatments of Coronaviruses

Medication	Study Design	Results	Comments
<b>Favipiravir (T-705)</b>	broad spectrum antiviral (RNA-dependent RNA polymerase inhibitor) with activity vs. SARS, West Nile, Zika, Yellow Fever, Chikungunya, Poliovirus and other that has been studied in severe influenza and Ebola and suggested as a treatment for pandemic influenza In addition to influenza		
<b>Galidesivir</b>	Antiviral with activity against COVID-19 and yellow fever virus – randomized, placebo controlled pharmacokinetic study – given as an IV infusion		
<b>Camostat mesilate</b>	serine protease inhibitor that may block entry of COVID-19 into cells with positive data in mice <a href="#">NCT04321096</a> , <a href="#">NCT04338906</a> (WITH HCQ) <a href="#">NCT04353284</a>		
<b>Nafamostat (RACONA study)</b>	RCT of continuous infusion of nafamostat vs. placebo		
<b>Mavrilimumab</b>	–Single dose IV in severe COVID (but not mechanically ventilated)		
<b>Gimsilumab</b>	–human monoclonal antibody that acts on GM-CSF (Roivant) in development for autoimmune diseases and malignancy		
<b>Leronlimab (PRO-140)</b>	CCR5 antagonist previously studied for HIV and cancer <a href="#">NCT04343651</a> phase 2 trial 700mg leronlimab vs. placebo		
<b>Arbidol</b>	–non-nucleoside broad-spectrum antiviral with immune-enhancing effect		
<b>Danoprevir</b>	–brand name Ganovo, and oral antiviral used for hepatitis C in China. Ongoing Phase 4 study in China of danoprevir+ritonavir as one of 5 experimental therapies. Comparators include interferon (Pegasys 180 mcg SQ weekly), Novaferon inhalation (cytokine gene derived protein), lopinavir/ritonavir or Chinese medicine + interferon inhalation –		
<b>T89</b>	– Effect of T89 on improving oxygen saturation and clinical symptoms in patients with COVID-19. Open-label, randomized trial of T89 or control for up to 14 days in addition to background treatment of antiviral, antibiotic, oxygen and traditional Chinese medicine. T89 is taken twice daily for 10 days		
<b>Aviptadil</b>	–Synthetic form of vasoactive intestinal polypeptide approved in Europe for several respiratory diseases and suggested as immunomodulator in ARDS given as titrated escalating infusion 50-150 pmol/kg/hr over 12 hours		
<b>Umifenovir</b>			
<b>CD424Fc</b>	SAC-COVID - biological immunomodulator in phase II/III studies in leukemia patients with severe GVHD. Will be given as a single dose 480mg in 100 mg NS over 60 minutes in patients with severe COVID-19		
<b>Defibrotide</b>	postulated to decrease inflammation and expression of adhesion molecules in the endothelium, leukocyte tissue infiltration and epithelia destruction and promote immune tolerance		
<b>Spain phase 2b trial</b>	of continuous infusion 25 mg/kg over 24 hours for 15 days vs. placebo		
<b>Angiotensin- (1-7) ATCO Trial</b>	– Phase 2/3 trial of infusion of angiotensin-(1-7) in patient with severe COVID-19 on mechanical ventilation		
<b>Piclidenoson 2 mg po bid PO</b>	on empty stomach added to standard care in hospitalized pts with COVID		
<b>Tradipitant ODYSSEY</b>	Phase 3 randomized double blind trial of tradipitant, a neurokinin-1 antagonist, 85mg orally BID in patients with severe or critical COVID		
<b>IFX-1</b>	single dose randomized open-label trial vs. standard care only in patients with severe COVID pneumonia		

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