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Nascent perspectives on COVID-19 treatments

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INTRODUCTION

As of March 2021, the outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), or COVID-19, has resulted in a global incidence of 11,844,672 cases, with corresponding mortality of 262,827 or a mortality rate of 2.2% (Johns Hopkins University of Medicine, 2021) [A]. Early detection and recognition of COVID-19 infections remain essential in determining disease severity and dictate whether pulmonary and pharmacologic treatments should be effective (Alhazzani et al., 2021 [M]; Bhimraj et al., 2021 [M]).

Diagnosis of COVID-19 is based on signs and symptoms and diagnosis by either reverse transcription polymerase chain reaction (PCR) or serology testing for COVID-19 antibodies with either enzyme-linked immunosorbent assay or rapid test (Hanson et al., 2020 [M]; FDA, 2020 [S]). For early diagnosis of COVID-19, there are currently two at-home diagnostic tests approved for Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA), one of which requires a prescription while the other is available over the counter (FDA, 2021a [S]; FDA, 201b [S]). For early diagnosis of COVID-19, there are currently two at-home diagnostic tests approved for Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA), one of which requires a prescription while the other is available over the counter (FDA, 2021a [S]; FDA, 2021b [S]). For early diagnosis of COVID-19, there are currently two at-home diagnostic tests approved for Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA), one of which requires a prescription while the other is available over the counter (FDA, 2021a [S]; FDA, 2021b [S]).

Based on the latest Infectious Diseases Society of America (IDSA) treatment guideline for COVID-19 (Bhimraj et al., 2021) [M], only remdesivir is recommended among the aforementioned anti-viral therapies due to possible association with mortality and morbidity benefits compare to the rates in China during the initial recognition of COVID-19. Remdesivir is FDA-approved for COVID-19 adult and pediatric patients 12 years of age and older and weighing at least 40kg. Despite the FDA approval and recommendation for the use of remdesivir by the IDSA, the lack of a control group in multiple clinical trials means it remains inconclusive whether the remdesivir monotherapy is associated with statistically significant benefit in mortality or morbidity (Grein et al., 2020 [c]; Goldman et al., 2020 [C]). As a result, the WHO recommends against the use of remdesivir for COVID-19, regardless of the severity of COVID-19 (WHO, 2020) [S]. Nevertheless, when used with specific medication such as corticosteroids and baricitinib, remdesivir has demonstrated positive clinical outcomes in COVID-19 patients (Alhazzani et al., 2021 [M]; Bhimraj et al., 2021 [M]).

Multiple pharmacologic treatment options are available for those diagnosed with COVID-19 and experiencing pulmonary and systemic signs and symptoms. They include anti-viral therapies such as chloroquine and hydroxychloroquine (SEDA-42, 294) with or without azithromycin (SEDA-40, 318; SEDA-42, 555), remdesivir (SEDA-42, 294), favipiravir and arbidol (SEDA-42, 294), and lopinavir-ritonavir (SEDA-39, 278; SEDA-41, 311), the supportive medication famotidine (SEDA-26, 294), anti-inflammatory medications such as dexamethasone (SEDA-39, 407; SEDA-40, 507; SEDA-41, 461), monoclonal antibodies such as tocilizumab (SEDA-42, 295), and convalescent plasma.

According to the most current IDSA COVID-19 treatment guideline (Bhimraj et al., 2021) [M], the supportive medication of famotidine is not recommended due to a lack of quality data. Famotidine-specific proposed mechanisms against COVID-19 include inhibition of COVID-19 3-chymotrypsin-like protease, and partial agonist of beta-arrestin, which mitigates histamine release and mast cell...
activation. In a single-center, retrospective study referenced by the IDSA (Bhimraj et al., 2021) [M], the famotidine group resulted in reduced composite of death or intubation (hazard ratio [HR] of 0.30; 95% confidence interval [CI] 0.11–0.80 \( P < 0.01 \)). Although famotidine is well-tolerated, the study was imbalanced as a result of its retrospective design, as the famotidine group comprised of 84 COVID-19 infected individuals within 24h of admission, while the group that did not received famotidine included 1536 patients. In addition, the composite outcome of death and intubation are not equivocal and are not reported separately by the investigators. Lastly, there have been no other clinical trials evaluating famotidine or any other medication within the same or similar class of medications, such as proton pump inhibitors. As a result, the IDSA recommends against the use of famotidine for both prophylaxis and treatment of COVID-19 infected patients, and suggests further studies is warranted.

According to both the IDSA guideline and Society of Critical Care Medicine (SCCM) COVID-19 management guideline (Alhazzani et al., 2021 [M]; Bhimraj et al., 2021 [M]), dexamethasone 6mg orally or intravenously daily for 10 days or until hospital discharge is recommended in patients requiring respiratory support only, with SCCM recommending the medication only in patients on invasive pulmonary interventions such as mechanical ventilation or extracorporeal membrane oxygenation (ECMO). On the other hand, IDSA recommends it in the criteria above as well as patients on non-invasive treatments, including oxygen delivered via nasal cannula. In the event dexamethasone is unavailable, both guidelines recommend utilizing equipotent glucocorticoids such as methylprednisolone sodium succinate with a daily dose of 32mg orally or intravenously or prednisone 40mg orally per day, despite limited studies evaluating the effectiveness of these agents with the different dosing regimen, and concern for increased risk of clinical thrombosis (Salton et al., 2020 [C]; Mishra & Mulani, 2021 [r]). Usage of corticosteroids in COVID-19 patients without the need for respiratory therapy is not recommended as it is associated with increased mortality (relative risk [RR], 1.22; 95% CI 0.93–1.61; \( P =0.14 \)) (Bhimraj et al., 2021 [M]).

There have been additional anti-viral, anti-inflammatory, and monoclonal antibodies pharmacologic therapies evaluated for COVID-19, and they include nitazoxanide, ivermectin, colchicine, bamlanivimab, etesevimab, and sarilumab. The Janus kinase (JAK) inhibitors including baricitinib, and ruxolitinib, may mitigate COVID-19 severe respiratory distress syndrome by inhibiting the interleukin- and granulocyte-macrophage colony-stimulating factor-mediated intracellular signaling pathway of cytokines (Stebbing et al., 2020) [H].

### THERAPEUTIC WINDOW

As mentioned, early detection and recognition of COVID-19 infections remain essential in determining disease severity and both pulmonary and pharmacologic interventions (Alhazzani et al., 2021 [M]; Bhimraj et al., 2021 [M]). Viral load is highest within 5–10 days from the date of initial exposure and infectivity, and depending on the patient’s immune system this may result in no symptoms, mild symptoms (e.g., fever, leukocytosis), moderate symptoms or inflammatory response (e.g., oxygen saturation of 94% or less, necessitating hospitalization and oxygenation therapy), or severe symptoms with significant inflammation, such as the development of acute respiratory distress syndrome, cytokine storm, or septic shock (Alhazzani et al., 2021 [M]; Bhimraj et al., 2021 [M]).

Immunosuppressive therapies such as corticosteroids, tubulin-inhibition therapy, and JAK inhibitors have demonstrated effectiveness in hospitalized patients with moderate and severe symptoms, and therefore should be used in the late hyperinflammatory stages of COVID-19 infection. Early usage of these therapies may predispose patients to unnecessary risk for toxicities, and increase mortality. For instance, in COVID-19 patients with mild symptoms, those that were administered dexamethasone 6mg orally or intravenously daily for 10 days had a higher relative risk for mortality than those that did not receive the medication, although this was not statistically significant (RR 1.22, 95% CI 0.93–1.61; \( P =0.14 \)).

Unlike immunosuppressive therapies, monoclonal antibodies may be indicated in both early or late stages of infection, since their mechanism of action against COVID-19 is through prevention of the virus from anchoring onto human alveolar cells, and mimicking, restoring, or enhancing the host’s immune system response (Alhazzani et al., 2021 [M]; Bhimraj et al., 2021 [M]). Based on the immunoenhancing effects of convalescent plasma, this therapy may also be utilized in either early or late stages of infection. However, the usage of plasma is associated with significant adverse events, including transfusion-related acute lung injury, transfusion-associated circulatory overload, and allergic transfusion reactions, although the incidence of all of these events combined is <1% of all transfusions.

Antiviral therapies may also be indicated in both early and late stages of infection in order to minimize viral load. With the exception of remdesivir in hospitalized COVID-19 patients with moderate-to-severe symptoms, studies published on prophylactic or treatment usage of antivirals such as chloroquine and hydroxychloroquine, lopinavir and ritonavir, or ivermectin have not demonstrated significant hospitalization avoidance or mortality benefits (Bhimraj et al., 2021) [M]. There is currently no
TREATMENT MEDICATIONS AGAINST COVID-19

Anti-viral therapies

Nitazoxanide

Nitazoxanide is an oral, broad-spectrum antiviral and antiparasitic medication effective against coronavirus, hepatitis B and C, influenza viruses, Cryptosporidium parvum, and Giardia lamblia. Its mechanism against SARS-Cov-2 is through inhibiting the replication of SARS-CoV-2 in Vero CCL81 cells (Wang et al., 2020) [H]. A multi-center, randomized, double-blind, placebo-controlled trial of adult patients who presented with COVID-19 symptoms for at least 3 days were either randomized 1:1 to nitazoxanide 500mg orally three times a day for 5 days or placebo (Rocco et al., 2020) [C]. Overall, 194 and 198 patients were given nitazoxanide and placebo, respectively, and there was no difference in symptoms between both groups upon completion of the 5-day course between both the treatment and placebo groups. There was statistical significant detection of a negative nasopharyngeal swab specimen for COVID-19 antigens for the treatment group (29.9% vs 18.2%; \(P = 0.009\)). The ongoing presence of symptoms despite significant reduction in viral load detection may be attributed to the systemic hyperinflammation that may have occurred already upon enrollment into the study (Lee et al., 2004) [C]. No significant adverse drug events were reported.

Ivermectin (SEDA-42, 312)

Ivermectin has demonstrated an in vitro reduction in COVID-19 viral load, although the exact mechanism is unknown (Caly, Druce, Catton, Jans, & Wagstaff, 2020) [E]. Lopez-Medina et al. (2021) [C] conducted a double-blind, randomized, single-site study in symptomatic, laboratory-confirmed COVID-19 adult patients, with patients either randomized to ivermectin 300micrograms/kg of body weight daily and orally \((n = 238)\) for 5 days or placebo \((n = 238)\). The study included only patients with mild disease, defined as not receiving oxygenation support, and were hospitalized or at home. There was no difference in median time to resolution of symptoms between both groups \((10 \text{ days [interquartile range IQR, 9–13] vs 12 days [IQR, 9–13]}\) for the ivermectin and placebo groups, respectively; HR of 1.07, \(P = 0.53\)). As a result, the IDSA guideline recommends against the use of ivermectin in hospitalized patients and outpatients (Bhimraj et al., 2021) [M], with additional clinical trials needed in COVID-19 patients.

Tubulin-inhibition therapy

Colchicine

The anti-inflammatory mechanism of colchicine via tubulin inhibition has been shown to reduce inflammatory lung injury in models of acute respiratory distress syndrome (Dupuis et al., 2020) [E]. A randomized, double-blind trial of non-hospitalized patients at least 40 years of age diagnosed with COVID-19 by PCR received either colchicine 0.5mg orally twice daily for 3 days, then once daily thereafter for 30 days or placebo (Tardif et al., 2021) [MC]. The primary efficacy endpoint was the composite of death or hospitalization for COVID-19 30 days of randomization. Although patients treated with colchicine were associated with lower incidence of the primary endpoint, it was not statistically significant \((\text{odds ratio [OR], 0.75; 95\% CI 0.57–0.99; } P = 0.04)\). The colchicine group had a greater incidence of diarrhoea than the placebo group \((13.7\% \text{ vs } 7.3\%, \text{ } P < 0.0001)\), although this was expected based on its neurogenic stimulation effect on the gastrointestinal tract. Beyond the gastrointestinal adverse effects, other serious events including pneumonia, dehydration, and pulmonary embolism were comparable between both the treatment and placebo groups. Despite the investigators’ conclusion that colchicine results in lower composite of death or hospitalization in COVID-19 outpatients, the medication did not show any statistically significant improvement in either endpoint of death \((\text{OR, 0.56; 95\% CI 0.19–1.67}}\) or hospitalization \((\text{OR, 0.79; 95\% CI 0.60–1.03}}\). In addition, the exclusion of patients under 40 years of age limits the external validity of the study.

Monoclonal antibodies

Bamlanivimab with or without etesevimab

Both bamlanivimab and etesevimab are neutralizing monoclonal antibodies derived from two different patients who successfully recovered from COVID-19 in North America and China, with both drugs binding onto the S1 subunit, N-terminal domain, various receptor-binding domain, and S2 subunit epitopes of the virus, including the resistant B.1.1.7 (United Kingdom) and B.1.351 (South Africa) variants by etesevimab (Jones et al., 2020) [E]; Shi et al., 2020 [E]). This is especially important to evaluate due to the emergence of various COVID-19 spike mutations towards the end of 2020 and the potential for viral drug resistance (Rambaut et al., 2020) [H]. Gottlieb et al. (2021) [C], conducted a randomized, multi-center phases 2 and 3 trial across.
the United States, including ambulatory, COVID-19 positive adult patients with one or more mild or moderate symptoms as defined by the FDA. The study had multiple groups, including a variety of intravenous dosing regimens of bamlanivimab monotherapy: 700 mg (n = 101), 2800 mg (n = 107), 7000 mg (n = 101), or in combination with intravenous etesevimab 2800 mg at a dose of 2800 mg (n = 112), or placebo (n = 156).

For the primary endpoint, the log viral load reduction by day 11 was lowest with the combination treatment (−4.37), follow by the 2800 mg monotherapy group (−4.08), placebo (−3.80), 700 mg monotherapy group (−3.72), and 7000 mg monotherapy group (−3.49); only the combination group compared to placebo resulted in a statistically significant reduction in viral load (95% CI, −1.00 to −0.14; P = 0.01). There was no clinically significant difference in baseline characteristics, including the severity of COVID-19 symptoms, between all the groups. COVID-19-related hospitalizations or emergency department visits by day 29 since randomization were similar between all treatment groups (1–2 events) and lower than placebo (9 events). Although immediate hypersensitivity reactions did occur in 9 patients, including 1 in the placebo group, all were mild reactions, not dose-dependent, and infusions were completed in all instances (Gottlieb et al., 2021) [C].

While the combination and monotherapy groups did result in lower COVID-19 hospitalizations and emergency department visits than the placebo group, the lack of statistically significant reduction in viral load by the monotherapy groups compared to the combination group, and the more effective viral load reduction with placebo compared to the highest monotherapy group questions the clinical outcomes impact of bamlanivimab with or without etesevimab. As a result, the IDSA guideline recommends against bamlanivimab monotherapy in both hospitalized patients and outpatients (Bhimraj et al., 2021) [M], although the guideline does not offer any comment on the combination therapy. One argument for the questionable efficacy of bamlanivimab with etesevimab may be attributed to both medications having reduced activity against the B.1.351 COVID-19 variant, although this variant remains rarely detected in the United States at the time of the study (NIH, 2021) [S]. In February 2021, the FDA issued an EUA for bamlanivimab 700 mg with etesevimab 1400 mg for outpatients with mild-to-moderate COVID-19. The lower than studied dosing is based on in-vitro pharmacokinetic and pharmacodynamic modeling (NIH, 2021) [S].

**Sarilumab**

Similar to tocilizumab (SEDA-42, 295), sarilumab is a monoclonal antibody that inhibits interleukin-6 receptors of the inflammatory pathway. An ongoing, open-label international study randomized critically ill adult patients with suspected or confirmed COVID-19 to either intravenous tocilizumab (8mg/kg, up to a maximum of 800 mg) for 1–2 doses or intravenous sarilumab (400 mg) as a single dose, or standard care as the control group (Gordon et al., 2021) [C]. The only two exclusion criteria are either imminent risk for death or a lack of commitment to fully support or prior participation in this study. Compare to the control group (n = 402), both tocilizumab (n = 353) and sarilumab (n = 48) results in greater odds of median organ support-free days, with an odds ratio of 1.64 (95% CI, 1.25–2.14) and 1.76 (95% CI, 1.17–2.91), respectively. Furthermore, the mortality rates were lower for both tocilizumab (28%) and sarilumab (22.2%) than the control group (35.8%), despite >80% of the control group utilizing corticosteroid, which has been shown to improve mortality in critically ill COVID-19 patients on respiratory support (Horby et al., 2020) [MC], although the study didn’t report on the median duration or dosing of the corticosteroid (Gordon et al., 2021) [C].

While the IDSA recommends tocilizumab for hospitalized, critically ill patients on either invasive or non-invasive respiratory support, the guideline does not offer any formal recommendation for sarilumab (Bhimraj et al., 2021) [M]. The rationale behind the lack of guidance is the small number of treated patients with the medication (n = 45) and no alternative published studies on determining the role of sarilumab at this time. Despite the role of tocilizumab in intensive care COVID-19 patients, the SCCM treatment guideline does not offer any recommendation for or against the use of sarilumab, or any other monoclonal antibodies, due to insufficient evidence (Alhazzani et al., 2021) [M].

**JAK kinase inhibitors**

**Baricitinib**

Through selective inhibition of JAK 1 and 2 enzymes, baricitinib reduces inflammatory response mediated by various interleukins and interferons, which is the basis for the multi-center, international, double-blind, placebo-control study by Kalil et al. (2021) [MC]. More specifically, baricitinib inhibits cytokines established to be elevated in severe COVID-19, including interleukin-10, interleukin-6, and interleukin-2, granulocyte-macrophage colony stimulating factors, and interferon-gamma. In addition, the medication prevents COVID-19 cell entry and infectivity through impairing adaptor protein complex 2-associated protein kinase 1. Hospitalized adult patients enrolled into the treatment group (n = 515) were given baricitinib 4 mg enteral daily for 14 days, along with remdesivir 200mg intravenous once as a loading dose on day 1, then 100mg intravenously once daily from days 2 to 10. On the other hand, patients in the control group (n = 518)
received remdesivir, and both groups were allowed to receive corticosteroids.

The primary outcome evaluated time-to-recovery in days for patients to achieve category 1, 2, or 3 on the eight-category ordinal scale by day 28; category 1 is defined as not hospitalized and no limitations of activities, category 2 is also not hospitalized yet limitation of activities and/or require home oxygen, category 3 is hospitalization but do not require supplemental oxygen or ongoing medical care, while category 8 means death. The secondary outcomes include mortality, and degree of respiratory support on selective days since enrollment from days 1 through 29. Overall, the baricitinib with the remdesivir-treated group had shorter median time-to-recovery days, with recovery defined as time-to-attain category 1 (not hospitalized, without activity limitations), 2 (not hospitalized but required home oxygen and/or have a limitation of activities), or 3 (hospitalized but do not required supplemental oxygen or no longer requiring any ongoing medical care) on the aforementioned ordinal scale compare to the control group (7 days vs 8 days, respectively; 95% CI, 1.01–1.32; \( P = 0.03 \)).

For the subgroup analysis, the greatest recovery rate of 1.51 (95% CI, 1.10–2.08) was patients receiving non-invasive mechanical ventilation at baseline at 10 days vs 18 days between the baricitinib and remdesivir group vs the control group, respectively. The next highest recovery rate were patients on mechanical ventilation or ECMO for the treatment group compared to the control group (rate of 1.08, 95% CI, 0.59–1.97). Interestingly, the rate is higher than for the 223 patients in this study who received corticosteroids (recovery rate of 1.06, 95% CI, 0.75–1.48). The 28-day mortality was lower in the treatment group at 5.1% compared to the control group at 7.9% (HR 0.65, 95% CI 0.39–1.09), with the greatest benefit observed in patients with a baseline ordinal scale of 5: hospitalized patient requiring supplemental oxygen.

For safety, as compared to the control group (3.1%), the baricitinib with remdesivir group were associated with similar venous thromboembolism (VTE) rate at 4.1% (95% CI, −1.3 to 3.3). Furthermore, the baricitinib-remdesivir group had a lower rate of new infections than the placebo group (5.9% vs 11.2%; 95% CI, −8.7 to −1.9, \( P = 0.003 \)). Patients who received any systemic glucocorticoid in this study after randomization had a higher incidence of new infection than patients who did not receive such treatment (25.1% vs 5.5%). However, the study doesn’t report on the median dose or duration of corticosteroid use. Both VTE and new infections were evaluated due to the black box warning for the risk of serious infections, malignancy, and thrombosis with baricitinib (Eli Lilly and Company, 2020) [S]. Baricitinib is FDA-approved for adult patients with moderate to severe active rheumatoid arthritis (RA), and there has been a question on whether the drug or the chronic disease of RA is attributed to the increased incidence of the black box events. A meta-analysis of 9 RA studies utilizing baricitinib was evaluated for VTE event incidence (Taylor et al., 2019) [R]. Overall, 3492 patients received baricitinib compared to placebo. There was no significant difference in VTE 0.6% vs 0% for the baricitinib and placebo groups, respectively, regardless of daily dose given (2mg, 0.5 per 100 patient-years or 4mg, 0.6 per 100 patient-years). Another meta-analysis evaluated the prevalence of treatment-emergent infections in RA patients treated with baricitinib, across 6 studies (Winthrop et al., 2020) [R]. The total patient-years exposure to either baricitinib 2 or 4mg was a median and maximum exposure of 2.6 and 6.1 years, respectively. The occurrence of serious infections was similar to placebo, with an incidence rate 3 per 100 patient-years.

The low incidence of both infections and thrombosis in long-term exposure to baricitinib compare to placebo in RA patients make it unlikely for the development of these adverse events with 14-day usage of baricitinib 4mg enterally daily for COVID-19 patients (Kalil et al., 2021) [MC]. It is unclear whether the recovery and mortality benefits reported by Kalil et al. (2021) [MC], are primarily attributed to either baricitinib or remdesivir, as both medications were use concurrently. As a result, the IDSA guideline recommends baricitinib with remdesivir in hospitalized patients only if they cannot or are contraindicated to receive corticosteroids (Bhimraj et al., 2021) [M]. The guideline also recommends baricitinib with remdesivir with corticosteroids only in the context of a clinical trial. The concern of utilizing all three medications simultaneously may increase the risk for infection, even though the actual risk for this occurrence has not been established (Bhimraj et al., 2021) [M].

**Ruxolitinib**

Despite being a JAK inhibitor similar to baricitinib, ruxolitinib is FDA-approved for different indications of polycythemia vera, myelofibrosis, and acute graft-vs-host disease (Incyte, 2020) [S]. Ruxolitinib was evaluated in a phase-3 clinical trial on determining whether it may reduce the incidence of death, respiratory failure requiring mechanical ventilation, or intensive care admission for patients 12 years and older with COVID-19 associated cytokine storm (Business Wire, 2020) [r]. The study result reported no difference in the above-mentioned endpoints compare to standard-of-care at 12% and 11.8%, respectively (OR, 0.91; 95% CI, 0.48–1.73; \( P = 0.769 \)). By Day 29 of therapy, there was no statistically significant difference in mortality or time-to-recovery. This may be due to the inclusion of patients between 12 and 17 years old since the risk for hospitalization and death are significantly lower than patients 18 years and older (CDC, 2021) [S].
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