Current Treatments for COVID-19

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Inpatient Treatments for COVID-19

Remdesivir: *200 mg IV x 1 day, followed by 100 mg IV for 4 days*

Mechanism of Action: Disrupts the virus' ability to multiply and infect more cells in the body. It does so through inhibition of viral replication through premature termination of RNA transcription. Its use can improve disease outcomes and reduce viral loads.[1]

Clinical Trial: In the ADAPTIVE COVID-19 trial, a multinational, randomized controlled trial that compared remdesivir to placebo, patients with moderate symptomology had greater clinical status later in disease when compared to placebo, and improved time to recovery. There was no observed benefit in patients not requiring supplemental oxygen, mechanical ventilation, or ECMO.[2]

Recommendations: NIH/IDSA guidelines recommend 200 mg IV for 1 day, followed by 100 mg IV for 4 days, or until hospital discharge, whichever comes first.[1,3] WHO guidelines recommend against routine use due to the results of the WHO Solidarity Trial – the evidence from their meta-analyses suggested no benefit.[4] Despite this, Remdesivir should still be used because of the statistically significant improved time to recovery and reduced length of hospitalizations in the Adaptive COVID-19 Treatment Trial, which contradicts the Solidarity Trial's results, and therefore NIH/IDSA guidelines still recommend.[16]

Duration of Treatment: In a recent open-label trial supported by Gilead Sciences, there was no significant difference in efficacy between 5 and 10-day courses, so patients should be limited to 5-day courses.[5]

Overall, it appears remdesivir does not provide an overall mortality benefit, but does reduce time to clinical improvement when given early in the course of illness and/or in patients with less severe disease. Duration of treatment between 5- and 10-day courses did not show a significant difference in efficacy. In crisis capacity settings with limited remdesivir supply, remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

Dexamethasone: *6 mg IV/PO daily for up to 10 days*

Mechanism of Action: Potent corticosteroid with predominately glucocorticoid effects and little to no mineralcorticoid action that increases the production of anti-inflammatory compounds and reduces the production of pro-inflammatory compounds.[1]

Clinical Trial: In the RECOVERY trial, those with moderate-severe disease (requiring supplemental oxygen, mechanical ventilation, or ECMO) had reduced mortality at 28 days than patients randomized to the standards of care; the greatest evidence was seen for those on MV. Among participants who did not require supplemental oxygen at enrollment there was statistically insignificant higher mortality associated.[5]

Recommendations: NIH/IDSA guidelines recommend dexamethasone IV/PO 6 mg daily for up to 10 days.[1,3] WHO guidelines recommend dexamethasone 6 mg QD for 7-10 days OR 50 mg of hydrocortisone IV q8hrs for 7-10 days.[7]

Duration of Treatment: Extended treatment should not be preferred as it inhibits the protective function of T cells and blocks B cells from making antibodies, leading to prolonged increases in plasma viral load. Dexamethasone's half-life is 36-48 hours so dosing is only once daily.[8]

Overall, it appears dexamethasone provides an overall mortality benefit, with the most prominent benefits seen in those on mechanical ventilation. Dexamethasone can be administered IV or PO at 6 mg daily for up to 10 days; extended treatment may prolong elevated plasma viral load. There was a trend (though statistically insignificant) towards higher morality when utilized in patients NOT requiring oxygen therapy.

Tocilizumab: *8 mg/kg (actual body weight) IV x 1 (max dose = 800 mg) and* **sarilumab:** *200 mg subq once*

Mechanism of Action: Interleukin-6 receptor antagonist that inhibits the release of cytokines and the associated pro-inflammatory state.[1]

Clinical Trial: In the COVACTA trial, 450 adults hospitalized with severe COVID-19-related pneumonia were randomized to receive tocilizumab or placebo. The trial failed to meet its primary endpoint or several key secondary endpoints including a lack of any mortality benefit, need for ICU care and/or ventilator use, and supplemental oxygen requirements.[9]

In the REMAP-CAP trial, 803 adults hospitalized with severe COVID-19-related pneumonia (admitted to the ICU and receiving respiratory or cardiovascular organ support) were randomized to receive tocilizumab (353), sarilumab (48), or control (402). Patients could also receive standard of care (dexamethasone and/or remdesivir). The trial has yet to be peer-reviewed, however preliminary results are promising. Hospital mortality was decreased (mortality was 28% for the tocilizumab group, 22.2% for the sarilumab group, and 35.8% in the control group). In addition, median organ support-free days were reduced for tocilizumab and sarilumab. Across secondary outcomes, tocilizumab and sarilumab were effective across 90-day survival, time to ICU and hospital discharge, and improvement in the WHO ordinal scale at day 14.[17]

Recommendations: IDSA/NIH have NOT updated their recommendations for these agents since the preliminary results of the REMAP-CAP trial were released. Prior to this release, they recommended against using tocilizumab unless under a clinical trial, since the results from the COVACTA trial were conflicting.[1,3]

Overall, it appears tocilizumab has potential benefit in the treatment of COVID-19. While the COVACTA trial and REMAP-CAP trial have conflicting data, the REMAP-CAP trial preliminary results look promising. These treatments are extremely costly, however reductions in ICU stays (secondary outcomes) and greater organ support-free days may compensate for this premium. Once peer reviewed, IL-6 receptor antagonists may become only the 2nd drug therapy (behind corticosteroid dexamethasone) to improve mortality outcomes.

Convalescent Plasma (CP): *neutralizing antibody titers of at least 1:160*

Mechanism of Action: Provides passive immunotherapy via pathogen neutralization; CP, which includes antibodies, is derived from people who have recovered from COVID-19. Postulated to have direct antiviral properties in those with active infection, reducing viral load.[1]

Clinical Trial: CP lacks sufficient data from well-controlled randomized clinical trials. Both the FDA and Mayo Clinic have performed retrospective, indirect evaluations of efficacy and have hypothesized that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes. There is still no standardization established for screening of donated CP, and oftentimes assays to assess titer quantity are not widely available. Use in expanded access programs often do not assess titer quantity prior to infusion.[1]

Recommendations: IDSA recommends limiting the use of CP for patients admitted to the hospital to the context of a clinical trial.[3] NIH states insufficient data to recommend either for or against the use.[1] CP is often not routinely stocked at hospitals and can take up to 24 hours to obtain, and any patient who receives CP should receive anticoagulation with enoxaparin.[3]

Overall, CP lacks sufficient data for use and efficacy is limited to titer quantity, which is often not assessed prior to infusion. Many institutions have utilized through EUA or clinical trials. Any patient who receives CP should, at a minimum, receive intermediate dose prophylaxis with enoxaparin.

Antithrombotic Therapy: *UF, LMWH, DOACs, or Warfarin* therapy + Aspirin*

Mechanism of action: COVID-19 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and d-dimers, and thus has been associated with increases in DVT and stroke risk.[1]

Recommendations: All adults who are admitted should receive VTE prophylaxis (UF, LMWH, DOACs, Warfarin*) in addition to ASA 81 mg. Warfarin is not evidenced in anticoagulation recommendations due to lack of evidence. Many clinicians still feel comfortable utilizing as long as INR and d-dimer are stabilized. If multiple doses are being held due to high/unstable INR, conversion to UF or DOACs are reasonable considerations. UF and LMWH are the preferred agents as they are easy to reverse, have a short half life, and minimal drug-drug interactions.[1]

Overall, all adults who are admitted should receive VTE prophylaxis, in addition to ASA 81mg. UF and LMWH are the preferred agents as they are easy to reverse, have a short half-life, and have minimal drug-drug interactions, though DOACs may also be utilizes. Warfarin is not evidenced in anticoagulation recommendations due to lack of evidence, though may clinicians feel comfortable with its use as long as the INR and d-dimer remain stabilized and doses are not routinely held.

Baricitinib (with remdesivir): *adults and pediatric patients (9+ years old): 4 mg daily; pediatric pts (2-9 years old): 2 mg daily*

Mechanism of Action: Janus kinase inhibitors are potent immunosuppressive agents, which interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins that are involved in vital cellular functions, including signaling, growth, and survival. This prevents the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6). Baricitinib also has theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry into and infection of susceptible cells.[10]

Clinical Trials: Combination of remdesivir & baricitinib was shown to reduce time to recovery within 29 days after initiating treatment compared to patients who received remdesivir alone. The odds of a patient's condition progressing to death or being ventilated at day 29 was also lower in the baricitinib group. The median time to recovery was 7 days, versus 8 days with remdesivir alone.[10]

Recommendation: FDA issued an EUA for the drug baricitinib, in combination with remdesivir, for treatment of COVID-19 in hospitalized patients (2 years and older) requiring supplemental oxygen, ECMO, or mechanical ventilation. Dosing is 4 mg daily for those 9+ years old and 2 mg daily for those <9 years old.[11] IDSA/NIH/WHO guidelines have not yet updated their guidelines to recommend for/against use.

Overall, baricitinib, in combination with remdesivir, may reduce time to recovery and reduce progression to death or requiring mechanical ventilation. Use has not been evaluated by major guidelines, though the FDA has issued an EUA for use in hospitalized patients requiring supplemental oxygen, ECMO, or mechanical ventilation.

Outpatient Treatments for COVID-19: Monoclonal Antibodies

Bamlanivimab: *700 mg IV infusion once over 60 minutes*

Mechanism of Action: Monoclonal antibodies are laboratory-made proteins that mimic the immune system's ability to fight off harmful antigens. Bamlanivimab is a monoclonal antibody that is specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells.[12]

Clinical Trial: In BLAZE-1, a phase two randomized, double-blind, placebo-controlled clinical trial, 465 non-hospitalized adults with mild to moderate COVID-19 symptoms received either bamlanivimab (309 patients) or placebo (156 patients within three days of obtaining a COVID+ result. The most important evidence that bamlanivimab may be effective came from the predefined secondary endpoint of COVID-19-related hospitalizations or emergency room visits within 28 days after treatment. For patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of bamlanivimab-treated patients on average compared to 10% in placebo-treated patients.[12]

Recommendation: FDA issues an EUA for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients (12 and up, ≥40kg) who are not currently hospitalized or requiring supplemental oxygen and who are at high risk of progressing to severe COVID-19 and/or hospitalization (those 65+ years old and/or who have certain chronic medical conditions). The effects on viral load and on reduction in hospitalizations and ER visits, and on safety, were similar in patients receiving any of the three bamlanivimab doses, so the lowest dose, 700 mg IV, is recommended.[13]

Casirivimab & Imdevimab: *1,200 mg of each mAb in a single IV infusion over 60 minutes*

Mechanism of Action: Casirivimab and imdevimab are monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells.[14]

Clinical Trial: In R10933-10987-COV-2067, a randomized, double-blind, placebo-controlled clinical trial, 799 non-hospitalized adults with mild to moderate COVID-19 symptoms received either casirivimab/imdevimab (533) or placebo (266). Viral load reduction in patients treated with casirivimab and imdevimab was larger than in patients treated with placebo at day 7. Predefined secondary endpoint of medically attended visits related to COVID-19, particularly hospitalizations and emergency room visits within 28 days after treatment, showed that for patients at high risk for disease progression, hospitalizations and emergency room visits occurred in 3% of casirivimab and imdevimab-treated patients on average compared to 9% in placebo-treated patients.[14]

Recommendation: FDA issued an EUA for casirivimab and imdevimab to be administered together for treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 and up, ≥40kg) who are at high risk for progressing to severe COVID-19 (those 65+ years old and/or who have certain chronic medical conditions). The authorized dosage is 1,200 mg of casirimab and 1,200 mg of imdevimab administered in a single infusion over 60 minutes.[15]

Bamlanivimab 700 mg and etesevimab 1,400 mg: in a single IV infusion over 60 minutes

Mechanism of Action: Bamlanivimab and etesevimab are neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2.[18]

Clinical Trial: In the phase 2/3 BLAZE-1 trial (NCT04427501), an ongoing randomized, double-blind, placebo-controlled clinical trial, and the Phase 2 BLAZE-4 trial (NCT04634409), an ongoing randomized, double-blind, placebo-controlled clinical trial, compared to placebo-treated patients, the participants receiving this dual monoclonal antibody therapy had a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or death from any cause. There were no deaths in the bamlanivimab plus etesevimab arm and 10 deaths in the placebo arm.[19]

Recommendation: On February 9, 2021, the FDA issued an EUA for Bamlanivimab and etesevimab to be administered together for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 and up, ≥ 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization.[18] The recommended dose is bamlanivimab 700 mg plus etesevimab 1,400 mg, and the treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset. Laboratory studies suggest that bamlanivimab and etesevimab have activity against the SARS-CoV-2 B.1.1.7 variant but have markedly reduced activity against the B.1.351 variant. At this time, the B.1.351 variant has rarely been detected amongst SAR-CoV-2 samples sequenced in the United States.[19]

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Treatments & Trials in the Pipeline

Oral Remdesivir

Matinas BioPharma Holdings Inc. plans to collaborate with the National Institute of Allergy and Infectious Diseases to test oral formulations of remdesivir in preclinical models.[1]

- Lipid nanocrystal (LNC) delivery technology enables the development of a wide range of difficult-to-deliver molecules.[1]
- The technology works by forming a cochleate using naturally occurring phospholipids and calcium, creating highly stable crystalline units with multiple layers to encapsulate the drug. This protects drug from water and harmful external elements. This cochleate is delivered into the body orally and can directly target clinically relevant cells, fusing with the cell membrane, and releasing the drug into the target cell due to the low intraceullar calcium environment.[2]
- This would require a license from Gilead for the use of remdesivir and a license from Matinas for the use of the LNC formulation.[1]

Synthetic Antibodies

Scientists from the Philadelphia-based Wistar Institute, the Perelman School of Medicine at the University of Pennsylvania, Indiana University, INOVIO, and AstraZeneca received a $37.6 million award from the federal government to develop special DNA-encoded monoclonal antibodies (DMAbs) to fight COVID-19[3]

- Proposed to act as genetic blueprints that that would help patients to product antibodies that target parts of the SARS-VoV-2 virus, as other monoclonal antibodies mechanistically do, however, this synthetic capability would be useful due to the rapid manufacturing ability, low cost of production, and temperature-stable storage and distribution.[3]

Ruxolitinib

Novartis provides update on RUXCOVID study of ruxolitinib for hospitalized patients with COVID-19

- Novartis announced that the Phase III RUXCOVID study evaluating ruxolitinib on top of standard of care (SoC) therapy compared to SoC treatment alone in patients with COVID-19 did not meet its primary endpoint[4].
- Initial data show there was no statistically significant reduction in the proportion of patients on ruxolitinib plus SoC therapy who experienced severe complications, including death, respiratory failure requiring mechanical ventilation or admission to the intensive care unit (ICU) by Day 29, compared to SoC alone.[4] The trial also did not show clinically relevant benefit among secondary and exploratory endpoints including mortality rate by Day 29, and time to recovery (no longer infected, or ambulatory with no or minimal limitations).[4]

MK-7110

Merck Announces Supply Agreement with U.S. Government for Initial Doses of Investigational Biological Therapy for the Treatment of Patients with Severe and Critical COVID-19[5]

- In September 2020, OncoImmune (recently acquired by Merck) reported topline findings from an interim efficacy analysis of a Phase 3 study evaluating MK-7110 for the treatment of patients with severe and critical COVID-19. An interim analysis of data from 203 participants (75% of the planned enrollment) indicated that hospitalized patients with COVID-19 treated with a single dose of MK-7110 showed a 60% higher probability of improvement in clinical status compared to placebo, as defined

by the protocol. The risk of death or respiratory failure was reduced by more than 50%. The study is ongoing.[5]

- MK-7110 COVID-19 Therapeutic candidate is a first-in-class recombinant fusion protein that targets the innate immune system, an immune modulator.[5]

Casirivimab & Imdevimab

Regeneron Announces Encouraging Initial Data from COVID-19 Antibody Cocktail Trial in Hospitalized Patients on Low-flow Oxygen[6]

- The primary clinical objective of this initial analysis was to determine if there was sufficient efficacy in these patients to warrant continuing the trial (i.e., futility analysis). The results passed the futility analysis ($p<0.3$ one-sided), as seronegative patients treated with the antibody cocktail had a lower risk of death or receiving mechanical ventilation (HR: 0.78; 80% CI: 0.51-1.2).
- The benefit was driven by results starting one week post-treatment, when the risk of death or receiving mechanical ventilation was reduced by approximately half with antibody cocktail treatment, based on a post-hoc analysis.
- A much larger trial will be required to rigorously characterize this effect. The ongoing UK-based RECOVERY trial will provide those answers. It has already enrolled more than 2,000 hospitalized patients in the part of the trial evaluating adding the antibody cocktail to standard-of-care compared to standard-of-care alone.[6]

Colchicine

The Montreal Heart Institute (MHI) announced that the COLCORONA clinical trial has provided "clinically persuasive results" of colchicine's efficacy to treat COVID-19.

- This is a phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of colchicine in adult patients diagnosed with COVID-19 infection and have at least one high-risk criterion. Approximately 6000 subjects meeting all inclusion and no exclusion criteria will be randomized to receive either colchicine or placebo tablets for 30 days outpatient.[7]
- **The results from this press release have yet to be peer reviewed, and the press release reports that the results "approached statistical significance" but did not meet significance.[7]**
- The press release stated the rate of hospitalization or death was 21% lower among patients who received colchcine compared to those who were randomly assigned to placebo.[7]

Ivermectin

In hospitalized patients with severe COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial. In outpatients with COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial.[8]

- Ivermectin is an anti-parasitic agent that is FDA-approved for onchocerciasis and strongyloidiasis and is used off-label for the treatment of many parasitic infections. Although it has *in vitro* activity against some viruses, it has no proven therapeutic utility. Ivermectin does have some *in vitro* activity against SARS-CoV-2, but concentrations needed to obtain the *in vitro* EC50 are considerably higher than those achieved in human plasma and lung tissue.
- Across all 5 RCTs, there were concerns due to lack of blinding of study personnel, which may lead to over- or under-estimates of treatment effects, particularly for subjective outcomes (e.g., symptom resolution, adverse events). Randomization was also a concern in two RCT, with one allocating all critically ill patients to the ivermectin arm, and another allocated participants based on odd or even registration numbers.[8]

Fluvoxamine

In a double-blind, randomized, fully remote (contactless) clinical trial, 152 non-hospitalized adults with confirmed severe acute respiratory syndrome coronavirus 2 infection, with COVID-19 symptom onset within 7 days and oxygen saturation of 92% or greater, received either fluvoxamine vs placebo.[9]

- Of 152 patients who were randomized (mean [SD] age, 46 [13] years; 109 [72%] women), 115 (76%) completed the trial. Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (absolute difference, 8.7% [95% CI, 1.8%-16.4%] from survival analysis; log-rank *P* = .009). The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events.[9]
- In this preliminary study of adult outpatients with symptomatic COVID-19, patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days. However, the study is limited by a small sample size and short follow-up duration, and determination of clinical efficacy would require larger randomized trials with more definitive outcome measures.[9]

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