# COVID-19 Advanced Therapies

Subjects: Allergy

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The coronavirus disease 2019 (COVID-19) pandemic, related to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a worldwide sudden and substantial burden in public health due to an enormous increase in hospitalizations for pneumonia with the multiorgan disease. Treatment for individuals with COVID-19 includes best practices for supportive management of acute hypoxic respiratory failure. Emerging data indicate that dexamethasone therapy reduces 28-day mortality in patients requiring supplemental oxygen compared with usual care, and ongoing trials are testing the efficacy of antiviral therapies, immune modulators and anticoagulants in the prevention of disease progression and complications, while monoclonal antibodies and hyperimmune globulin may provide additional preventive strategies. Consensus suggestions can standardize care, thereby improving outcomes and facilitating future research.

Keywords: SARS-CoV-2 ; severe acute respiratory syndrome ; antiviral agents ; systemic corticosteroids ; monoclonal antibodies ; passive immune therapies ; anticoagulation ; antibiotics

## 1. Introduction

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China and shortly spread throughout China, followed by an increasing number of cases in other countries throughout the world [1]. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019, while the virus that causes COVID-19 was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2].

Until now, most viral infections tended to be treated with supportive care, and in some cases, antiviral therapy is used. As therapeutic interventions seem mandatory, at least in severe and critical COVID-19, in this study, we will review and discuss the supportive care along with specific, advanced approaches based on severity profile. For hospitalized patients, the standard of care mainly consists of adequate hydration, oxygen therapy, antibiotic use and thrombotic prophylaxis, accompanied by vital sign observation. Antivirals, along with immunomodulatory treatments, are more likely to be effective in the second and third phases of the disease [3].

## 2. Anti-Viral Agents

Several previously published studies have indicated that remdesivir, a viral RNA-dependent RNA polymerase inhibitor, may show some effectiveness against SARS-CoV-1, MERS-CoV and SARS-CoV-2 [4][5]. In the early ACTT1 trial [6], 1062 patients underwent randomization, 541 of whom were assigned to remdesivir and 521 to placebo, respectively. In that trial, reductions in recovery time and length of hospital stay (the primary outcomes of the study) were shown, from 15 to 10 days (rate ratio for recovery 1.29, 95% CI 1.12–1.49; $p < 0.001$) and from a median of 17 days to 12 days, respectively, while other secondary endpoints also showed positive benefits. However, no benefit on clinical recovery was observed in patients who received remdesivir at an advanced stage of the disease (symptoms >10 days) or in those who entered the study when they were already on mechanical ventilation or extracorporeal membrane oxygenation (recovery rate ratio 0.98, 95% CI 0.70–1.36). Goldman et al., in a SIMPLE-Severe study [7], demonstrated similar clinical improvement (≥2 points, in a 7-point ordinal scale) by day 14 with remdesivir given for 5 days versus 10 days in patients with severe COVID-19: 65% of patients in the 5-day group improved their clinical status versus 54% in the 10-day group ($p = 0.14$ for the baseline-adjusted difference between arms).

Lopinavir, an HIV type 1 aspartate protease inhibitor, combined with ritonavir, has been previously shown to reduce the risk of adverse clinical outcomes and decrease the viral load in patients with SARS, as compared to historical controls [8][9]. However, three randomized trials, RECOVERY [10], SOLIDARITY [11] and a randomized, open-label Chinese trial [12], showed no effect of lopinavir–ritonavir combination on mortality in SARS-CoV-2 patients, while no other benefits were evident for various endpoints, including time to clinical improvement, viral load, viral clearance, discharge from hospital within 28 days and the need for invasive mechanical ventilation. Adverse events, including serious ones, were not

increased, despite the known adverse event profile and drug–drug interactions of the lopinavir–ritonavir combination. [13][14].

Danoprevir is a potent hepatitis C virus (HCV) protease (NS3/4A) inhibitor, which was approved in 2018 in China for the treatment of hepatitis C. A small (n = 11) open-label, single-arm study evaluated the effects of danoprevir, boosted by ritonavir, in moderate COVID-19 patients hospitalized for pneumonia without respiratory failure. The primary endpoint of the study was the rate of composite adverse outcomes (defined as SPO2 ≤ 93% without oxygen supplementation, PaO2/FiO2 ≤ 300 mm Hg or a respiratory rate ≥30 breaths/min without supplemental oxygen), while the efficacy was also evaluated.

## 3. Antibiotics

In a Wuhan-based study reporting outcomes and treatment for 191 patients hospitalized for COVID-19 [15], 50% of the deaths were imputable to secondary bacterial infections. The reported incidence of potential respiratory bacterial co-infections upon admission was 3.5% in several cohort studies, while secondary bacterial infections during hospitalizations occurred up to 15% of patients [16]. A systematic review on bacterial and fungal co-infections in COVID-19 patients reported an overall percentage of 8% of bacterial infections at any time during hospitalization, with the most common pathogens reported being: *S. aureus*, *H. influenzae*, *S. pneumoniae* and *K. pneumoniae*, while *Mycoplasma* spp., *Enterobacter ales*, *A. baumannii* and *P. aeruginosa* have also been reported [17]. Most bacterial pneumonias detected early enough can be safely and effectively treated with antibiotics [18]. Thus, antibiotics appear to be a crucial defense against mortality in COVID-19 patients. Broad-spectrum antibiotics are being widely used in hospitalized patients with COVID-19 pneumonia and/or signs of bacterial co-infection, with the most common antibiotic classes prescribed being fluoroquinolones, followed by macrolides, β-lactam/β-lactamase inhibitors and cephalosporins [19]. However, as excessive antibiotic use drives the emergence of antibiotic-resistant bacteria and antimicrobial resistance is by now a burning issue, antibiotics should be used with caution in COVID-19 patients. In daily practice, it is difficult to distinguish viral from bacterial pneumonia. As to what should be done with antibiotic therapies in the COVID-19 era, several guidelines have been additionally published, such as those from the Netherlands, the UK (NICE guidelines) and South Africa, as well as experts' recommendations [17][20][21][22].

There appears to be a consensus among these documents that in the presence of suspected bacterial co-infection, particularly in most severe cases, local and/or national guideline-concordant antibiotics should be commenced. The 2020 Surviving Sepsis Campaign guideline on COVID-19 recommended treating critically ill patients admitted to the ICU with empiric antibiotic therapy within 1 h while waiting for the test results. If all the cultures are negative after 48–72 h of incubation, it may be reasonable to discontinue antibiotics, whereas if the microbiological results indicate the presence of a bacterial co-infection, antibiotic treatment may be able to be narrowed depending on the findings and should be continued for 5–7 days [23]. The evidence based on bacterial infections in COVID-19 is currently limited; therefore, large, randomized, controlled trials on the epidemiology of bacterial infections and antibiotic use in COVID-19 are needed.

## 4. Systemic Corticosteroids

The most consistent outcome of corticosteroids' efficacy in COVID-19 has been reported in the Randomized Evaluation of COVID-19 therapy (RECOVERY) trial [24], which enrolled 6425 hospitalized patients with COVID-19, 2104 of whom were randomized to receive dexamethasone (6 mg per day for 10 days) plus the standard of care or the standard of care alone. A significant reduction in mortality was reported with dexamethasone for both groups overall (22.9% versus 25.7%; $p < 0.001$), as well as in patients receiving oxygen (23.3% versus 26.2%) or mechanical ventilation (29.3% versus 41.4%) at randomization. However, no clear effect on mortality was manifested for patients with no supplementary oxygen requirements (17.8% versus 14.0% in dexamethasone and standard of care, respectively), with a pooled odds ratio for all patient subgroups of 0.70 (95% CI 0.48–1.01) and a greater mortality benefit in response to the treatment with dexamethasone for patients with a longer duration of symptoms. Still, the trial showed a numerically shorter median duration of hospitalization (12 versus 13 days), a statistically significant decreased need for invasive mechanical ventilation (risk ratio 0.77; 95% CI, 0.62 to 0.95) and a greater probability of discharge alive in 28 days (rate ratio 1.10; 95% CI 1.03–1.17) with dexamethasone plus the standard of care versus the standard of care alone. Similarly, the CoDEX trial [25] evaluated 299 patients with moderate or severe COVID-19-related ARDS (CARDS), concluding that dexamethasone plus standard of care resulted in a statistically significant increase in the number of days alive and in days free of mechanical ventilation over 28 days versus standard of care alone.

In conclusion, corticosteroids have been shown to significantly reduce mortality in randomized trials, with significantly different benefits according to disease severity based on the requirement for oxygen or mechanical ventilation, justifying different recommendations for different subgroups of patients. Unanswered questions regarding corticosteroids include the optimal molecule, timing, dosing and scheme, as well as the duration of treatment. Although concerns about potential adverse events due to their use seem reasonable, the consistency of results from most trials is reassuring about their risk-benefit profile.

## 5. Anticoagulants

The incidence of thromboembolic events in COVID-19 appears to be considerably higher compared to other critically ill or ARDS patients or in other respiratory virus infections known to lead to a procoagulant state [26]. A report from the American Society of Hematology states that the prevalence of DVT ranges from 1.1% among not critically ill patients to 69% among ICU patients [27]. The exact mechanism that leads to COVID-19 coagulopathy remains unclear, but several pathways have been proposed, such as complement-mediated thrombogenesis, the cytokine storm leading to neutrophil recruitment and NETosis and pneumonia mediated hypoxia, that stimulates platelet and neutrophil adhesion to endothelial cells while suppressing tissue factor pathway inhibitor and fibrinolytic pathways [28][29]. Disease severity in COVID-19 is associated with the prolongation of the prothrombin time (PT), international normalized ratio (INR) and variably by a trend toward shortened activated partial thromboplastin time (aPTT) [30].

SARS-CoV-2. For non-hospitalized patients with COVID-19, the CDC proposes that anticoagulants should not be initiated for VTE prevention, unless other indications for the therapy exist or the patient is participating in a clinical trial [31]. Regarding thrombotic prophylaxis in hospitalized COVID-19 patients, relative agreement exists in the recommendations of several national and international scientific societies: the CDC recommends LMWH or UFH; the WHO recommends prophylactic daily LMWHs or twice-daily subcutaneous unfractionated heparin (UFH); the American Society of Hematology (ASH) suggests LMWH over UFH unless the risk of bleeding outweighs the risk of thrombosis; the American College of Cardiology (ACC) recommends that 40 mg of Enoxaparin daily or a similar LMWH can be administered with consideration of SC heparin (5000 IU twice to three times per day) in patients with renal dysfunction [30]. If pharmacological prophylaxis is contraindicated, mechanical VTE prophylaxis should be considered in immobilized patients [30].

Concerning the duration of therapeutic anticoagulation, ACF recommends at least a 3-month course for patients who start anticoagulation for a presumed provoked thrombus from the inflammatory state of CAC but did not have imaging available for confirmation. Similarly, the ACCP and SCC-ISTH recommend a minimum of 3 months of anticoagulation in those patients with confirmed PE or proximal DVT. The ISTH-IG, ASH, ACC and CDC do not mention any recommendations or suggestions regarding the duration of therapeutic anticoagulation [32].

## 6. Anti-Inflammatory Agents

Several non-randomized cohort studies indicated the efficacy of anakinra, an IL-1 receptor antagonist, in moderate to severe COVID-19 pneumonia [33][34][35][36][37][38]. However, there is an essential need for randomized trials to confirm the benefit of anakinra in patients with COVID-19 pneumonia, hypoxia, respiratory failure and signs of progression into the third phase of the disease, dominated by hyperinflammation and an uncontrolled inflammatory response [39].

In the TOCIBRAS study, an open-label, randomized trial that included 438 adults hospitalized with severe or critical COVID-19 pneumonia was conducted. Patients were randomized to receive either tocilizumab plus the standard of care versus a placebo plus the standard of care [40]. Standard of care included hydroxychloroquine, azithromycin, corticosteroids and antibiotics but not remdesivir, as that antiviral agent was not available. The TOCIBRAS trial was prematurely interrupted because of increased mortality at day 15 in the tocilizumab group compared to the control group (17% versus 3%; OR 6.42; 95% CI 1.59–43.2). Tocilizumab therapy was also not associated with an improvement in mechanical ventilation or death at day 15 (28% versus 20%, 95% CI, 0.66–3.66, $p = 0.32$).

The BACC Bay randomized, double-blind, placebo-controlled trial [41] enrolled 243 adult patients and evaluated the efficacy of tocilizumab in patients with moderate COVID-19 pneumonia (body temperature >38 °C, pulmonary infiltrates and need for supplemental oxygen in order to maintain an oxygen saturation ≥ 92%). Patients were allocated to receive tocilizumab 800 mg intravenously plus the standard of care (including antiviral therapy, hydroxychloroquine and glucocorticoids) or the standard of care. In this trial, the early use of tocilizumab did not reduce the need for intubation or mortality by day 28 (11.2% of the patients in the tocilizumab group were intubated or died versus 10.6% in the standard of care group; hazard ratio 0.83 95% CI, 0.38–1.81, $p = 0.64$).

## 7. Passive Immune Therapies

Therapeutic products containing anti-SARS-CoV-2 neutralizing antibodies obtained from recovered patients (convalescent plasma, hyper-immune anti-SARS-CoV-2 globulin) or artificial ones (monoclonal antibodies, Mabs) have attracted increased interest since the beginning of the COVID-19 pandemic.

Several manufacturers are developing neutralizing anti-SARS-CoV-2 monoclonal antibodies that target the S-protein. As of June 2021, two Mabs combinations, bamlanivimab/etesevimab and casirivimab/imdevimab (also called REGN-COV2), and the Mab sotrovimab have been issued an FDA EUA for outpatients with mild/moderate COVID-19 and an increased risk of progression to severe disease [42]. Similarly, the European Medicines Agency (EMA) recommended a marketing authorization for the use of bamlanivimab/etesevimab and casirivimab/imdevimab combinations [4] and for the use sotrovimab [5] or regdanvimab [43] in high-risk patients with early-stage COVID-19, while the FDA-issued EUA for the bamlanivimab monotherapy was recently revoked, mainly because of concerns about the resistance of the new SARS-CoV-2 variants [42]. It should be emphasized that these therapies are not currently recommended for the treatment of hospitalized patients with severe COVID-19 disease, though research is ongoing. However, a recent trial testing bamlanivimab in hospitalized patients demonstrated that the addition of REGEN-COV to usual care reduces 28-day mortality of inpatients without detectable anti-SARS-CoV-2 antibodies at the baseline compared to usual care [44]. Even more interestingly, a study conducted during the autumn of 2020 found that bamlavinimab reduced the risk of infection by SARS-CoV-2 among residents and staff in skilled nursing and assisted-living facilities with positive cases, paving the way for the evaluation of Mabs as preventive tools [45].

## 8. Conclusions

Although the treatment of viral respiratory infections has traditionally been mostly supportive, the COVID-19 pandemic profoundly disrupted human activities and claimed millions of lives worldwide, thus forcing an unprecedented effort of health scientists, international organizations and pharmaceutical companies to develop novel, disease-specific therapies. According to the current model of COVID-19 pathobiology and in agreement with early clinical observations, it seems likely that antiviral agents, including antibody-based therapies, are more effective when administered early in the disease course, and they are anticipated to prevent the progression to severe/critical disease, which will lead to reductions in the need of hospitalization and mortality. During more progressed stages of the disease, when lung and systemic inflammation are driving the clinical course of COVID-19, anti-inflammatory and immuno-modulating agents might be required. Research aiming to discover more effective agents and the proper patient population to treat with them is underway.

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