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Editorial

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Emerging Treatments for COVID-19

Maria A Arruda*

Research Development Manager at University of Nottingham, Nottingham, Nottinghamshire, United Kingdom

***Corresponding author:** Maria A Arruda, Research Development Manager at University of Nottingham, Nottingham, Nottinghamshire, United Kingdom; E-mail: Maria.Arruda@nottingham.ac.uk

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Editorial

An oral antiretroviral protease inhibitor currently approved for the treatment of HIV Infection. Lopinavir/ritonavir has been used in clinical trials for the treatment of COVID-19. Results from one small case series found that evidence of clinical benefit with lopinavir/ritonavir was equivocal. A randomized controlled trial of 200 patients with severe disease found that treatment with lopinavir/ritonavir plus standard care (i.e., oxygen, noninvasive and invasive ventilation, antibiotics, vasopressors, renal replacement therapy, and extracorporeal membrane oxygenation, as necessary) was not associated with an decreased time to clinical improvement compared with standard care alone, and 28-day mortality was similar in both groups. Preliminary results from the UK RECOVERY trial found that there is no beneficial effect of lopinavir/ritonavir in hospitalized patients with COVID-19. There was no significant difference in 28-day mortality, risk of progression to mechanical ventilation, or duration of hospital stay between the two treatment arms (lopinavir/ritonavir versus usual care alone), and the results were consistent in different subgroups of patients. Lopinavir/ritonavir may increase the risk of bradycardia, especially in older, critically ill patients. Lopinavir/ritonavir should only be used in the context of a clinical trial.

Convalescent plasma from patients who have recovered from viral infections has been used as a treatment in previous virus outbreaks including SARS, avian influenza, and Ebola virus infection. Clinical trials to determine the safety and efficacy of convalescent plasma that contains antibodies to SARS-CoV-2 in patients with COVID-19 are ongoing. A randomized controlled trial found that convalescent plasma added to standard treatment did not significantly improve time to clinical improvement within 28 days in patients with severe or life-threatening disease. However, the trial was terminated early and may have been underpowered to detect a clinically important difference. A systematic review of five studies found that convalescent plasma may reduce mortality in critically ill patients, have a beneficial effect on clinical symptoms, and reduce viral load. A meta-analysis and systematic review with a total of 5444 patients found that the use of convalescent plasma reduced mortality, increased viral clearance, and resulted in clinical improvement in patients with COVID-19; however, the evidence is of low quality and further randomized controlled trials are required. A preprint (not peer reviewed) of an open-label, multicenter, expanded access program study of over 35,000 patients suggested that convalescent plasma lowered mortality in hospitalized patients when given within 3 days of diagnosis; however, there was no placebo group in this trial. The FDA has classified convalescent plasma as an investigational product (available via clinical trials, an expanded access program, or a single-patient emergency investigational new drug application), and has published guidance on the administration and collection of convalescent plasma from patients who have recovered from COVID-19. There is currently insufficient evidence to recommend either for or against the use of convalescent plasma for the treatment of COVID-19. The Infectious Diseases Society of America recommends convalescent plasma only in the context of a clinical trial. The authors of a Cochrane rapid review were uncertain as to whether convalescent plasma is beneficial for hospitalized patients with COVID-19. The completed studies were of poor quality, and the results could be related to natural progression of the disease or to other treatments the patient receives. There is limited information regarding adverse effects and very low-certainty evidence for safety in patients with COVID-19.

Intravenous immune globulin (IVIG) is being trialed in some patients with COVID-19. A retrospective study of 58 patients with severe COVID-19 found that IVIG, when used as an adjuvant treatment within 48 hours of admission, may reduce the use of mechanical ventilation, reduce hospital/intensive care unit stay, and reduce 28-day mortality; however, this study had several limitations. There is currently insufficient evidence to recommend IVIG for the treatment of COVID-19. The National Institutes of Health guidelines panel recommends against the use of non-SARS-CoV-2-specific IVIG for the treatment of COVID-19 except in the context of a clinical trial.

SARS-CoV-2 monoclonal antibodies have the potential to be used for prophylaxis and treatment of COVID-19. Recombinant, fully human monoclonal neutralizing antibodies, such as JS016 and LY-COV555, are in development. These antibodies bind to the SARS-CoV-2 surface spike protein receptor binding domain, which blocks the binding of the virus to the angiotensin-converting enzyme-2 (ACE2) host cell surface receptor. Both antibody treatments have started phase 1 studies. Novel multi-antibody cocktail therapies (e.g., REGN-COV2) are also in clinical trials for prophylaxis or treatment.

IL-6 receptor antagonist monoclonal antibodies (e.g., tocilizumab, sarilumab, siltuximab) are being trialed in COVID-19 patients for the treatment of virus-induced cytokine release syndrome. These drugs are already approved in some countries for other indications. A retrospective cohort study found that clinical improvement and 28-day mortality were not statistically different between tocilizumab and standard of care. However, other studies have found that the use of tocilizumab was associated with significantly shorter duration of vasopressor support, reduced risk of noninvasive mechanical ventilation, and a reduction in mortality in patients with severe or critical disease. A meta-analysis of 7 retrospective studies found that there is no suggestion that tocilizumab provides any additional benefit for patients with severe disease; however, this was based on low-quality evidence and the study had many limitations. Trials of sarilumab have been halted in the US as the drug failed to reach primary and key secondary end points.

Anakinra, an interleukin-1 inhibitor, is being trialed in COVID-19 patients for the treatment of virus-induced cytokine release syndrome. It is already approved in some countries for other indications. Addition of high-dose intravenous anakinra to noninvasive ventilation and standard care (which included hydroxychloroquine and lopinavir/ritonavir) in COVID-19 patients with moderate to severe acute respiratory distress syndrome and hyperinflammation was associated with a higher survival rate at 21 days in a small retrospective study. A small prospective cohort study found that anakinra significantly

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reduced the need for invasive mechanical ventilation and mortality in patients with severe disease. A small retrospective case series found that anakinra could be beneficial in patients with cytokine release syndrome when initiated early after the onset of acute hypoxic respiratory failure. The National Institutes of Health guidelines panel states that there is currently insufficient evidence to recommend either for or against the use of anakinra for the treatment of COVID-19. The National Institute for Health and Care Excellence in the UK states that there is no evidence available to determine whether anakinra is effective, safe, or cost-effective for treating adults and children with secondary hemophagocytic lymphohistiocytosis triggered by SARS-CoV-2 or a similar coronavirus.

Mavrilimumab, an antigranulocyte–macrophage colony-stimulating factor receptor-alpha monoclonal antibody, was associated with improved clinical outcomes compared with standard care in nonmechanically ventilated patients with severe disease and systemic hyperinflammation in a single-center prospective cohort study.

Janus kinase inhibitors (e.g., fedratinib, ruxolitinib, baricitinib) are currently in clinical trials for the treatment of COVID-19-associated cytokine release syndrome. The National Institutes of Health guidelines panel recommends against the use of Janus kinase inhibitors for the treatment of COVID-19 except in the context of a clinical trial.

Stem cell therapy is being investigated to treat patients with COVID-19 in clinical trials. It is thought that mesenchymal stem cells can reduce the pathologic changes that occur in the lungs, and inhibit the cell-mediated immune inflammatory response. The National Institutes of Health guidelines panel recommends against the use of mesenchymal stem cells for the treatment of COVID-19 except in the context of a clinical trial. Adipose-derived mesenchymal stem cells have been approved by the FDA for the treatment of severe COVID-19.

The BCG vaccine is being trialed in some countries for the prevention of COVID-19, including in healthcare workers. There is some evidence that BCG vaccination prevents other respiratory tract infections in children and older people mediated by induction of innate immune memory. However, there is no evidence to support its use in COVID-19, and the WHO does not recommend it for the prevention of COVID-19.

An experimental small molecule that inhibits AXL kinase. Bemcentinib has previously demonstrated a role in the treatment of cancer, but has also been reported to have antiviral activity in preclinical models, including activity against SARS-CoV-2. It was the first candidate to be selected as part of the UK's Accelerating COVID-19 Research and Development (ACCORD) study. The study has stopped recruiting new patients into the trial due to the reduction of new COVID-19 cases in the UK. Patients already recruited will continue on treatment as per the study protocol.

Angiotensin-II receptor antagonists such as losartan are being investigated as a potential treatment because it is thought that the angiotensin-converting enzyme-2 (ACE2) receptor is the main binding site for the virus. However, some experts believe that these drugs may worsen COVID-19 due to overexpression of ACE2 in people taking these drugs.

Various other antiviral drugs (monotherapy and combination therapy) are being trialed in patients with COVID-19 (e.g., oseltamivir, darunavir, ganciclovir, favipiravir, baloxavir marboxil, umifenovir, ribavirin, interferon, leronlimab). There is no evidence to support the use of umifenovir. Triple therapy with interferon beta-1b, lopinavir/ritonavir, and ribavirin has been tested in hospitalized COVID-19 patients in a small open-label randomized phase 2 trial. Patients who received triple therapy had a significantly shorter median time to a negative nasopharyngeal swab result compared with the control group (lopinavir/ritonavir only). Patients had mild to moderate disease at the time of enrolment. The National Institutes of Health guidelines panel recommends against the use of interferons for the treatment of severe or critically ill patients, except in the context of a clinical trial. The PRINCIPLE trial in the UK is currently evaluating three treatment strategies in older people (people ages over 65 years, or people ages over 50 years with an underlying health condition): usual care alone; usual care plus azithromycin; and usual care plus doxycycline.

Ivermectin, a broad-spectrum antiparasitic agent, has been shown to be effective against SARS-CoV-2 in vitro. It is unclear whether the doses necessary to achieve antiviral activity against SARS-CoV-2 are attainable in humans. Numerous registered clinical studies of ivermectin, either alone or in combination with other drugs (e.g., doxycycline, hydroxychloroquine), are ongoing in many countries for the treatment or prevention of COVID-19. Further research in randomized controlled trials is necessary.

Vitamin C supplementation has shown promise in the treatment of viral infections. High-dose intravenous vitamin C is being trialed in some centers for the treatment of severe COVID-19. There is no evidence to support or refute the use of vitamin C in the treatment of patients with COVID-19; however, a substantial number of trials are ongoing. The National Institutes of Health guidelines panel states that there is insufficient data to recommend either for or against vitamin C.

Vitamin D supplementation has been associated with a reduced risk of respiratory infections such as influenza in some studies. Vitamin D is being trialed in patients with COVID-19. However, there is no evidence to recommend vitamin D for the prophylaxis or treatment of COVID-19 as yet. The UK National Institute for Health and Care Excellence states that while there is no evidence to support taking vitamin D specifically to prevent or treat COVID-19, it does recommend that all people should take a vitamin D supplement daily as per UK government advice to maintain bone and muscle health during the pandemic, especially if they are not getting enough sun exposure due to shielding or self-isolating. The National Institutes of Health guidelines panel states that there is insufficient data to recommend either for or against vitamin D.

There is emerging evidence that gut dysbiosis may have a role in the pathogenesis of COVID-19. Probiotics may represent a complementary approach for the prevention or treatment of mucosal damage or inflammation through the modulation of gut microbiota; however, further research is required.

Traditional Chinese medicine is being used in patients with COVID-19 in China according to local guidelines and as part of clinical trials.

Preliminary evidence suggests that hyperbaric oxygen treatment has been successfully used to treat deteriorating, severely hypoxemic patients with severe COVID-19.

Studies indicate that nitric oxide may help to reduce respiratory tract infection by inactivating viruses and inhibiting their replication in epithelial cells. The FDA has approved an investigational drug application for inhaled nitric oxide to be studied in a phase 3 studies of

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up to 500 patients with COVID-19. Other studies are currently recruiting.

A synthetic form of vasoactive intestinal peptide (also known as RLF-100) has been granted an expanded access protocol (which makes the treatment available to patients who have exhausted approved therapies and who are not eligible for the current clinical trial of aviptadil) for the treatment of respiratory failure in patients with COVID-19. Intravenous and inhaled formulations are currently in phase 2 and 3 clinical trials in the US.

A selective bradykinin B2 receptor antagonist. A small exploratory case-control study of 9 people found an association between the administration of icatibant and improved oxygenation, suggesting that administration in the early stages of disease when patients are hypoxic may be beneficial. Treatment strategies that target the kallikrein-kinin system require further investigation in randomized trials for patients with COVID-19.