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REVIEW

Treatment of COVID-19: a review of current and prospective pharmacotherapies

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread and have grave health and socioeconomic consequences worldwide. Researchers have raced to understand the pathophysiological mechanisms underpinning the disease caused by SARS-CoV-2 so that effective therapeutic targets can be discovered. This review summarises the key pharmacotherapies that are being investigated for treatment of COVID-19, including antiviral, immunomodulator and anticoagulation strategies.

Key words: Anticoagulation, Antivirals, COVID-19, Immunomodulator

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to have a devastating impact on global healthcare systems and economies. Case numbers continue to rapidly rise in 2021, and deaths are now nearly 2.6 million (World Health Organization, 2021).

SARS-CoV-2 belongs to the coronavirus family of single-stranded RNA viruses that can cross species barriers and cause illness ranging from the common cold to more severe diseases such as severe acute respiratory syndrome and Middle East respiratory syndrome. Transmission of SARS-CoV-2 is believed to occur through respiratory droplets. Although the pathogenesis of the pulmonary manifestations remains poorly defined and knowledge of factors affecting disease severity is limited, underlying illnesses such as diabetes, cardiovascular diseases, hypertension, cancer and older age are associated with poorer outcomes (Huang et al, 2020). Patients can present with a wide range of clinical severity from asymptomatic to a severe form of interstitial pneumonia, which may progress to acute respiratory distress syndrome, multi-organ failure and death (Wang et al, 2020a).

Current strategies for pharmacotherapies are centred around three main areas: antiviral agents to prevent viral replication, immunomodulators to attenuate the dysregulated host immune response seen in severe disease, and treatments to counter the hypercoagulable state that leads to a high rate of thrombotic complications. This articles reviews the evidence for current and prospective drug candidates to treat COVID-19.

Antiviral strategies in COVID-19

Viral replication requires several processes that hijack host cell machinery, including endocytic fusion at the plasma membrane, uncoating and release of the viral genome into the cytosol, transcription and translation of viral RNA, and release via Golgi apparatus vesicle formation as a mature virion. Elucidating the biochemical processes underpinning the SARS-CoV-2 replication life cycle could pave the way for identification of targets for drug therapies. Owing to the time-critical need to find effective antivirals, attention has also turned to drug repurposing, where existing treatments are redeployed to combat SARS-CoV-2.

Currently approved antivirals for COVID-19

Remdesivir

Remdesivir inhibits viral replication by stalling RNA synthesis. Its active metabolite, remdesivir triphosphate, competes with endogenous adenosine triphosphate for incorporation into elongating RNA strands, causing termination of RNA synthesis (Kokic et al, 2021).

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The adaptive COVID-19 treatment trial (ACTT-1) was a randomised controlled trial in 1062 hospitalised patients sponsored by Gilead (Beigel et al, 2020). It reported a 4-day shorter recovery time for remdesivir (11 vs 15 days, $P<0.001$) compared with placebo. The benefits were mainly seen in the subgroup of patients receiving only low-flow oxygen. There was no significant difference in mortality between patients given remdesivir and those who received placebo. The Department for Health and Social Care later authorised remdesivir for emergency use in May 2020.

Conflicting preliminary results were published by the World Health Organization-sponsored SOLIDARITY trial (Pan et al, 2020). In 2750 patients assigned to a 10-day course of remdesivir, there was no significant difference observed in inpatient hospital mortality compared to the standard of care. There was also no significant difference in time to discharge or clinical deterioration requiring mechanical ventilation.

The World Health Organization (2020) issued a recommendation against the use of remdesivir in hospitalised patients. Given the high cost, many feel that there is currently weak evidence to support policy decisions to offer remdesivir, particularly in resource-limited settings where its price may worsen existing health inequities.

Antiviral therapies in phase II and III clinical trials

Bamlanivimab

The spike (S) protein of SARS-CoV-2 binds to the human angiotensin-converting enzyme 2 (hACE2) receptor through its receptor binding domain, using serine proteases as entry activators (Hoffman et al, 2020). Bamlanivimab is a neutralising IgG1K monoclonal antibody that binds to the receptor binding domain of the S protein, preventing attachment to the hACE2 receptor. The ACTIV-3 trial testing the co-administration of remdesivir and bamlinivimab was halted early, as the treatment arm did not show any improvement in clinical outcomes on day 5 compared to placebo (ACTIV-3/TICO LY-CoV555 Study Group, 2020).

However, results from other trials suggest that bamlanivimab might have greater efficacy earlier in the disease course. The BLAZE-I clinical trial assigned 452 outpatients to receive three different dose strengths of bamlanivimab or placebo (Chen et al, 2021). Patients who received the intermediate dose had an accelerated decline in viral loads by day 11 and lower rates of hospitalisation.

The pharmaceutical company Eli Lilly issued a press release stating that bamlanivimab reduces the risk of contracting COVID-19 in a randomised controlled trial enrolling residents and staff in an American care home (Lilly, 2021). Among residents ($n=299$), a significantly lower frequency of symptomatic COVID-19 was observed in those who received bamlanivimab (odds ratio 0.2, $P=0.00026$). This trial provides encouraging preliminary evidence for bamlanivimab efficacy in the prevention and early treatment of COVID-19 in a cohort of clinically vulnerable patients that have been hard hit by outbreaks of the disease.

Ivermectin

Ivermectin is a widely available and inexpensive antiparasitic drug that has demonstrated significant antiviral activity in vitro against numerous RNA viruses (Heidary and Gharebaghi, 2020). An in vitro study reported a 5000-fold reduction in SARS-CoV-2 RNA levels after infected Vero/hSLAM cells were incubated with ivermectin 5 µmol for 48 hours (Caly et al, 2020).

A retrospective observational cohort study undertaken in four Florida hospitals reviewed the charts of COVID-19 patients treated with and without ivermectin (Rajter et al, 2021). Univariate analysis showed lower mortality in the ivermectin group (15% vs 25.2%, odds ratio 0.52, $P=0.03$), and was lower in patients with severe disease (38.8% vs 80.7%, $P=0.001$).

Multiple randomised controlled trials are ongoing, but researchers in Latin America are struggling to recruit patients who are not already taking ivermectin as there has been widespread unchecked use of the medication after it was publicly endorsed by a number of health ministries, including those in Peru and Bolivia (Mega, 2020). Scientists have cautioned against the use of ivermectin outside of clinical trials pending more robust evidence.

Immunomodulators in COVID-19

Innate immune cells recognise pathogen-associated molecular patterns expressed after viral invasion of host cells. This triggers pathways mediating the release of pro-inflammatory cytokines that attract B and T cells to the site of infection. The presence of regulatory pathways means that, in most individuals, the immune response is attenuated as the B and T cells clear the pathogen. In a proportion of patients who develop severe disease as a result of SARS-CoV-2, there appears to be dysregulation of the immune response leading to exaggerated release of pro-inflammatory cytokines that induce tissue damage. This cytokine release syndrome can manifest clinically with development of diffuse alveolar damage, septic shock and multi-organ failure.

Cytokine profiling of patients with severe COVID-19 includes elevated levels of interleukin (IL)-2, IL-7, IL-6, IL-1, granulocyte colony-stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and tumour necrosis factor-α (Wang et al, 2020b). Lower lymphocyte counts (in particular CD4 T cells), and higher levels of ferritin and C-reactive protein on admission have also been shown to be associated with severity of disease (Qin et al, 2020). The association of poor clinical outcomes and immunopathology has raised the prospect of immunomodulation as a treatment strategy in COVID-19.

Approved immunomodulator treatments

Dexamethasone

The use of corticosteroids in acute respiratory distress syndrome has been the subject of numerous randomised controlled trials and meta-analyses and remains contentious (Steinberg et al, 2006; Meduri et al, 2016). Glucocorticoids had been used to treat viral pneumonia caused by Middle East respiratory syndrome and severe acute respiratory syndrome but there was a lack of sufficiently powered trials to provide convincing evidence for a beneficial effect. In this context, there were guarded expectations for the use of steroids to treat COVID-19.

The RECOVERY trial provided convincing evidence for the benefit of corticosteroids in patients with moderate to severe COVID-19 disease requiring oxygen (The RECOVERY Collaborative Group, 2021a). A total of 2104 patients received dexamethasone 6 mg daily for a median duration of 7 days. Compared to usual standard of care (n=4321), 28-day mortality was significantly lower in patients on mechanical ventilation (29.3% vs 41.4%). The incidence of death was also lower in those receiving supplementary oxygen, but not among those not receiving any respiratory support at randomisation.

The mortality benefit of corticosteroids in COVID-19 is likely to be influenced by optimal timing in the disease course. Further studies are needed to elucidate the effect of varying timing and dosing, and to assess the effect in those that may be more vulnerable to ill effects from high-dose steroids, for example patients with hypertension or poorly controlled diabetes, or older patients.

Enhanced corticosteroid regimens

Severe COVID-19 pneumonitis is characterised by progressive parenchymal involvement on radiology and an inflammatory state. The use of enhanced corticosteroid administration is an evolving area of clinical practice.

Extrapolating from experience of managing interstitial lung injury, short-term steroid dose escalation (or 'pulsing') may benefit selected patients with an inflammatory phenotype, often radiologically characterised by a ground glass opacification or organising pneumonia pattern. The optimum choice and dose of corticosteroid in this setting remains unclear and should be an area of focus for future research.

In a small randomised controlled trial of 68 hypoxic patients (SpO_2 <90%) who were not intubated, methylprednisolone was administered at 250 mg/day for 3 days and showed a significant reduction in mortality (Edalatifard et al, 2020). Two large systematic reviews have identified that acute corticosteroid administration has a mortality benefit in patients with severe disease, but heterogeneity of studies and lack of details on dosing made it difficult to conclude the benefit conferred by higher or lower doses (Sterne et al, 2020; Cano et al, 2021).

Anti-interleukin 6 monoclonal antibodies

Tocilizumab and sarilumab are monoclonal antibodies designed to block both soluble and membrane-bound IL-6 receptors. IL-6 has diverse downstream immunological effects and is thought to be a key player in the immunopathology of cytokine release syndrome. As well as its use in rheumatoid arthritis and juvenile idiopathic arthritis, tocilizumab is approved for the treatment of chimeric antigen receptor T cell (CAR-T)-induced cytokine release syndrome (Kotch et al, 2019).

The REMAP-CAP randomised controlled trial has published data in a preprint article on the effect of tociluzimab and sarilumab within 24 hours of admission to intensive care (Gordon et al, 2021); 353 patients received the former and 8 the latter. The study found a significant decrease in organ support-free days within the first 3 weeks in the tocilizumab group (median of 10 vs 0 in the placebo arm). Hospital mortality was also lower (28% vs 36%, P=0.03).

Encouraging results from a randomised controlled trial in which 2022 patients received tocilizumab have been released in a preprint from the RECOVERY researchers (Horby et al, 2021) – 28-day mortality was significantly reduced in the treatment arm (29% vs 33%, P=0.007). Among patients not on invasive ventilation at time of randomisation, tocilizumab reduced the risk of progressing to intubation or death from 38% to 33%.

Immunomodulator pharmacotherapies under trial

Baricitinib

Baricitinib is an orally administered Janus kinase (JAK) 1 and 2 specific inhibitor used to treat rheumatoid arthritis. Richardson et al (2020) proposed a rationale for its use in COVID-19 through inhibition of the JAK-STAT signalling pathway, which is used by multiple cytokines that have a key role in cytokine release syndrome. They hypothesised that it may also affect cellular entry of SARS-CoV-2 through its inhibitory effects on AP2-associated protein kinase, a known regulator of endocytosis.

The ACTT-2 trial evaluated baricitinib plus remdesivir against placebo in 1033 hospitalised patients (Kalil et al, 2021). The investigators saw a modest effect on the primary outcome of median time to recovery, which was more pronounced in patients on high-flow oxygen or non-invasive ventilation (10 days vs 18 days). Baricitinib also reduced the need for invasive ventilation (10% vs 15% in control arm). Areas for further research should include the effect of adding baricitinib to dexamethasone.

The RECOVERY trial added baricitinib as a treatment arm in January 2021 and will hopefully shed light on the effect in hospitalised patients with more severe disease.

Colchicine

Colchicine has been identified as a potentially useful treatment in COVID-19 as a result of its diverse anti-inflammatory effects, in addition to its inhibition of the assembly of microtubules that play a role in the intracellular transport of viral particles. The Montreal Heart Institute has released a preprint publication of the results of the COLCORONA trial in 4488 non-hospitalised patients randomised to receive a 30-day course of colchicine or placebo (Tardif et al, 2021). The treatment arm saw a reduction in the composite end-point of death or hospitalisation (4.6% vs 6.0%). This statistic was primarily driven by a reduction in hospitalisations, with absolute numbers for mortality low in both groups (5 deaths vs 9). The incidence of gastrointestinal adverse events was 23.9% in the colchicine group compared to 14.8% in the placebo group. The RECOVERY trial added colchicine to its trial in November 2020 and it is hoped that this will provide data on its efficacy in hospitalised patients.

Convalescent plasma

Convalescent plasma has been used in several pandemics, including the H1N1 influenza outbreak, Ebola and SARS-CoV (Cheng et al, 2005). There was initial optimism that passive antibody therapy could give a short-term strategy for providing immediate immunity. Mechanisms of action were postulated to be via direct neutralisation of the virus with antibodies, reduction of the serum cytokine response and regulation of coagulation cascades (Rojas et al, 2020).

In August 2020, the Food and Drug Administration issued emergency use authorisation for COVID-19 convalescent plasma. The decision was largely based on a preprint retrospective correlational study in 35 000 patients, that reported those who received higher titres of antibody in COVID-19 convalescent plasma tended to have lower mortality (Joyner et al, 2021).

Enthusiasm for COVID-19 convalescent plasma has been tempered by disappointing preliminary results from large randomised controlled trials. REMAP-CAP (2021) released a statement that recruitment of critically unwell patients had been paused because the results in 912 participants showed that there was very low probability (2.2%) that use of convalescent plasma reduces the number of days in intensive care or mortality. A statement from the RECOVERY trial investigators shortly after also announced that recruitment to test COVID-19 convalescent plasma had also been halted as no mortality benefit had been found overall or in any specific cohorts (The RECOVERY Collaborative Group, 2021b).

Anticoagulation and antiplatelet therapeutic strategies

Hypercoagulability as a sequela of pro-inflammatory cascades is a major contributor to increased mortality in patients with severe COVID-19. Cohort studies have shown a significantly increased incidence of thromboembolic events in hospitalised patients (Nopp et al, 2020). Case series documenting autopsy findings showed high incidence of pulmonary embolism, deep vein thrombosis, pulmonary arterial thrombosis and microvascular thrombi (Wichmann et al, 2020). Significant coagulopathy was observed, characterised by raised D-dimer, fibrin degradation product levels and prothrombin time, and was associated with poor prognosis (Tang et al, 2020).

Vascular endothelial cells express the ACE-2 receptor in large numbers, and viral entry by SARS-CoV-2 is hypothesised to cause severe endothelial damage (Varga et al, 2020). There is extensive interplay between the immune response and the coagulation cascade, which differentiates the immunothrombosis seen in COVID-19 from the typical formation of pulmonary emboli (Iba et al, 2020). Conway and Pryzdial (2020) have also proposed complement-mediated mechanisms by which SARS-CoV-2 may cause thromboinflammation.

These findings have made anticoagulation a key strategy in limiting complications from venous thromboembolism and microthrombosis in COVID-19.

What is the evidence for anticoagulation in COVID-19?

A retrospective study of 4389 hospitalised patients looked at the relationship between prophylactic and therapeutic dose low-molecular-weight heparin with mortality, intubation and major bleeding (Nadkarni et al, 2020). The researchers found that both therapeutic and prophylactic doses of anticoagulants reduced mortality by about half. Those being treated with anticoagulation also had 31% fewer intubations.

The HESACOVID trial randomised 20 patients on mechanical ventilation to therapeutic or prophylactic dose enoxaparin (Lemos et al, 2020). They found significant improvement in gas exchange (as measured by PaO_2:FiO_2) in the therapeutic dose group, with a higher ratio of successful liberation from mechanical ventilation.

The NIH Activ Trial has suspended enrolment of critically ill patients in three trials evaluating therapeutic dose anticoagulation (NIH Activ, 2021). Pre-publication data have indicated that anticoagulation in patients requiring intensive care did not significantly decrease organ-support free days or mortality compared to prophylactic dose. They also found an increased incidence of major bleeding events. However, interim results supported the use of therapeutic anticoagulation in patients with moderate severity disease, with a decrease in requirement for organ support and in mortality.

What is the current guidance for anticoagulation?

Current National Institute for Health and Care Excellence (2020) guidance recommends prophylactic dose low molecular weight heparin for hospital inpatients with COVID-19, and consideration of intermediate dosing for patients on advanced respiratory support.

Key points

- Therapeutic strategies in COVID-19 include antivirals, immunomodulators to attenuate the dysregulated cytokine response in severe disease and anticoagulation to reduce the risk of venous thromboembolism and microthrombi.
- Antivirals reduce viral propagation by inhibiting viral binding and endocytosis to the host cell, or by disrupting viral RNA transcription and translation. Remdesivir has had conflicting results from randomised controlled trials on its effects on time to recovery and mortality. Promising antivirals include bamlinivimab and ivermectin.
- Dexamethasone is the only immunomodulator therapy currently widely used to treat COVID-19. Encouraging data have emerged from trials of anti-IL-6 monoclonal antibodies and baricitinib. Randomised controlled trials investigating convalescent plasma have not yet shown any mortality benefit.
- Anticoagulation likely reduces mortality in hospitalised COVID-19 patients. Further trials are needed to assess the optimal intensity of anticoagulation, and the benefits of thromboprophylaxis post-discharge.

The American Society of Haematology issued a recommendation that critically unwell patients who do not have confirmed or suspected venous thromboembolism should receive prophylactic intensity anticoagulation over intermediate or therapeutic intensity regimens (Cuker et al, 2021).

Locally, the authors' guidelines advise intermediate dose, twice-daily dosing of heparin for critically unwell patients. In view of prolonged recovery and increased incidence of venous thromboembolism after discharge, the authors advocate extended thromboprophylaxis for 2–6 weeks post-discharge (Kumar et al, 2020). Direct oral anticoagulants may be preferred in the outpatient setting for ease of administration.

Antiplatelet therapy in COVID-19

Another area of interest is antiplatelet therapy, in view of its antiplatelet aggregation, anti-inflammatory effects, and possible antiviral properties. A retrospective cohort study in 412 patients where 98 received aspirin found an independent association with decreased risk of mechanical ventilation and in-hospital mortality (adjusted hazard ratio 0.53, 95% confidence interval 0.31–0.90; Chow et al, 2020).

There are ongoing randomised controlled trials evaluating the use of antiplatelets, including the RECOVERY trial which added aspirin as a treatment arm in November, and the C-19-ACS trial evaluating the effects of clopidogrel.

Conclusions

A year on from the beginning of the pandemic, there appear to be cautious hopes for its resolution with the rolling out of vaccination programmes. However, there is still an urgent need for effective pharmacotherapies to prevent severe disease and limit long-term complications from COVID-19. The treatment landscape is diverse and rapidly evolving. In the authors' opinion, effective pharmacotherapy is likely to require a multifaceted approach that encompasses antivirals early in disease to prevent viral replication, immunomodulators for the hyperinflammatory state seen in later stages of the disease, and anticoagulation to prevent the sequelae of venous thromboembolism and microthrombi.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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