NOVEL CORONAVIRUS DISEASE 2019 PHARMACOLOGICAL TREATMENTS: A REVIEW

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Abstract

The COVID-19 pandemic has caused an extraordinary need and challenge to identify effective therapeutic options for prevention and treatment. In this review, we summarize the major findings in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral characteristics and the novel coronavirus disease 2019 (COVID-19) pathophysiology, clinical presentation and outcomes. We then proceed to explain the mechanisms of action, outcomes, and adverse events identified for the front-running pharmacological treatments currently being used and/or investigated namely Remdesivir, Chloroquine/Hydroxychloroquine, Lopinavir/Ritonavir, Tocilizumab, and convalescent plasma.

Keywords: Coronavirus, Pandemics, Clinical Pharmacology.

Background

In January 2020, a new coronavirus was identified in China and has since spread worldwide, causing a pandemic. This novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially associated to a wet market in the city of Wuhan in China.[1] As of today, it has already infected more than 7 million people and accounted for more than 400 000 deaths worldwide.[2]

SARS-CoV-2 is the eighth known human coronavirus, the same family of SARS-CoV and MERS-CoV viruses that were associated with global emergencies (albeit on a smaller scale) in 2002 and 2012, respectively. Coronavirus disease 2019 (COVID-19) is the acute respiratory disease caused by SARS-CoV-2. Six months after the beginning of the pandemic, there is better understanding of the modes of transmission and pathophysiology of the disease. There is a wide spectrum of clinical presentations and the burden of this illness has been tremendous on the healthcare systems across

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the world. Researchers are attempting to elucidate the pathophysiology of the disease and propose therapies and clinical management strategies to guide the fight against COVID-19 around the world. In this review, we will briefly go over what is known about SARS-CoV-2, the pathophysiology of COVID-19 and its clinical course to then present the leading therapies being investigated to treat COVID-19 at the moment.

Viral characteristics

Coronaviruses are positive-sense single-stranded RNA viruses with three major surface proteins: spike (S), membrane (M), and envelope (E). Its linear genome has a 5' cap and a 3' poly-A tail which makes it fit to be directly translated as a messenger RNA after release into the infected cell.

The spike (S) glycoprotein is a class I fusion protein that binds the receptors on and fuses with host cells' membranes.[3] It has been found to be the target of neutralizing antibodies synthesized by the infected host.[4] The M protein is the most abundant surface protein and is believed to be responsible for the shape of the virion. Finally, the E protein is a transmembrane protein found to have many functions. Specifically, SARS-CoV E protein was found to be necessary for pathogenesis. The M and E proteins interact to form the viral envelope.

Other less-abundant proteins encoded by the viral genome are the nucleocapsid (N) protein inside the virion and the hemagglutinin-esterase (HE) on the surface of a subset of β-coronaviruses[3] to which SARS-CoV-2 belongs.[5]

Transmission

The primary means of transmission for SARS-CoV-2 is through exposure to respiratory droplets[6] from an infected individual and environmental contamination such as surface contamination. The possibility of aerosol[7] as well as non-respiratory specimen transmission[8] is still being investigated. The basic reproductive number (R_0) of SARS-CoV-2, which is the average number of people one infected person can potentially infect, is around 2.2.[9] Control measures aim to reduce that number below 1.

The infectious period of COVID-19 has been estimated to last for 9 days, 2 days before the onset of symptoms, and until 7 days after. In fact, 44% of transmitted cases were found to have been infected during the asymptomatic period of infection and positively related to family clusters. The incubation period of the virus is around 5.2 days.[10] The lag time between infection and seeking medical care allows for viral spread and potential infection of contacts during the initial stages of the illness when the viral load is highest. This creates a challenge for identifying and isolating the cases and their close contacts during the early stages of COVID-19.

Pathophysiology

To infect a cell, SARS-CoV-2 first attaches, via its S glycoproteins, to the angiotensin-converting enzyme 2 (ACE2) receptors on the membrane of the host cell.[11] ACE2 are found on many human cells, specifically lung and intestine epithelial cells.[12] The S glycoprotein is then cleaved into S1 and S2 subunits by proteases like furin and trypsin. Another cleavage event of the S2 subunit releases a fusion peptide and mediates virus and host membrane fusion followed by release of the virus genome into the cytoplasm. The viral RNA is directly translated by the host cell's translational machinery. RNA is replicated by a viral polymerase, packaged into newly synthesized virions and released from the infected cell.[11]

SARS-CoV-2 infection damages epithelial cells and induces the synthesis of GM-CSF known to activate NK and T cells as well as interleukin-6[13] part of the Th2-induced humoral immune profile response. This means that the virus is polarizing the host's immune response to an antibody-dominating one which is usually unfavorable for an intracellular infection. SARS-CoV-2 causes fever, respiratory symptoms and hypoxia and may further trigger an acute inflammatory cytokine storm. Apoptotic activity like the Fas-FasL[14] or TNF-related apoptosis-inducing ligand (TRAIL) pathways[15] may be the reason behind lymphopenia found in many COVID-19 patients. Viral particles and RNA were also identified in peripheral blood and lymphoid tissue which means that SARS-CoV-2 could

directly infect T cells.[16] The degree of lymphopenia was found to be positively associated with the severity of the disease[17] and increases the risk of secondary infection.[18]

Clinical features

Early studies from China indicated that the majority (80%) of COVID-19 infections result in mild to moderate illness, while around 20% are severe infections that require hospitalization, with 5-8% of all cases needing ICU care.[19] Several risk factors including older age and underlying diseases have been associated with increased risk of death.[20]

The major clinical features of COVID-19 are pneumonia with abnormal chest CTs, fever, cough with or without sputum production, lymphopenia, dyspnea, and myalgia or fatigue. Patients may also present with headaches, hemoptysis, gastrointestinal symptoms (nausea, vomiting, diarrhea), or anosmia and ageusia with or without fever.[16,21,22,23]

Patients with comorbidities, especially cardiovascular disease, obesity, diabetes, chronic respiratory disease, hypertension, and cancer were found to have worse outcomes than COVID-19 patients with no preexisting conditions.[22] The strongest risk factors for critical illness, on the other hand, are an O_2 saturation < 88%, a troponin level >1, a CRP level >200, and a D-dimer level >2500.[24]

The most common complications are viral sepsis, acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury, and secondary infection.[18,21] It is worth noting that the respiratory status of a COVID-19 patient can decompensate very quickly and that the duration between the onset of symptoms and invasive ventilation ranges from 12.0 to 19.0 days.[18]

Clinical course of disease

The mortality rate for severe cases, particularly those who are critically ill, is quite high. It is important to identify reliable predictors of disease severity to positively affect the course of illness. A number of risk factors are associated with worse prognosis of COVID-19 such as cardiovascular diseases, diabetes, hypertension and obesity, with immune suppression also contributing to increased morbidity and mortality. Recent studies from different cohorts of patients have identified several factors, including viral load, lymphocytes percentage, C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin (PCT) as warning indicators of prognosis in COVID-19 patients.[25] However, it is still unclear which of these factors are the most sensitive and reliable indicators for predicting the prognosis of COVID-19 at the early stage.

COVID-19 progression is divided into three stages: the early infection phase, the pulmonary phase, and the hyperinflammation phase. The immune response to the virus is predominant in the first phase, characterized by mild and non-specific symptoms like fever and dry cough as well as lymphopenia and neutrophilia. The pulmonary phase marks the transition between the viral immune response phase and the host inflammatory response phase. It is characterized by shortness of breath that can progress to hypoxia. Clinical signs include abnormal chest imaging, elevated liver transaminases, and low to normal procalcitonin. The third stage is dominated by the host inflammatory response and may manifest itself via acute respiratory distress syndrome (ARDS), systematic inflammatory response syndrome (SIRS), and/or cardiac failure. High levels of inflammatory signals (CRP, IL-6, LDH, D-dimer, ferritin), troponin, and NT-proBNP indicate the onset of this phase.[19]

Pharmacological treatment options for COVID-19

During the viral response phase, the main approaches to therapy include reducing immunosuppression, tackling symptomatic management in a timely manner, and avoiding the excessive use of corticosteroids. During the host's inflammatory response phase, corticosteroids, human Ig, and IL-2, IL-6, JAK inhibitors might be used. Antivirals like remdesivir, anti-malarial agents such as chloroquine and hydroxychloroquine, as well as convalescent plasma transfusions may be used throughout the three stages of COVID-19 illness.[19]

Therapeutic options are divided into antivirals and

adjunct treatments and can target different lines of attack including viral entry (camostat mesylate), membrane fusion (arbidol), proteolysis (lopinavir/darunavir), or viral RNA replication (ribavirin, remdesivir, favipiravir).[26] In this review, we will focus on the leading pharmacological treatment options for COVID-19 being investigated today (Figure 1).

Remdesivir

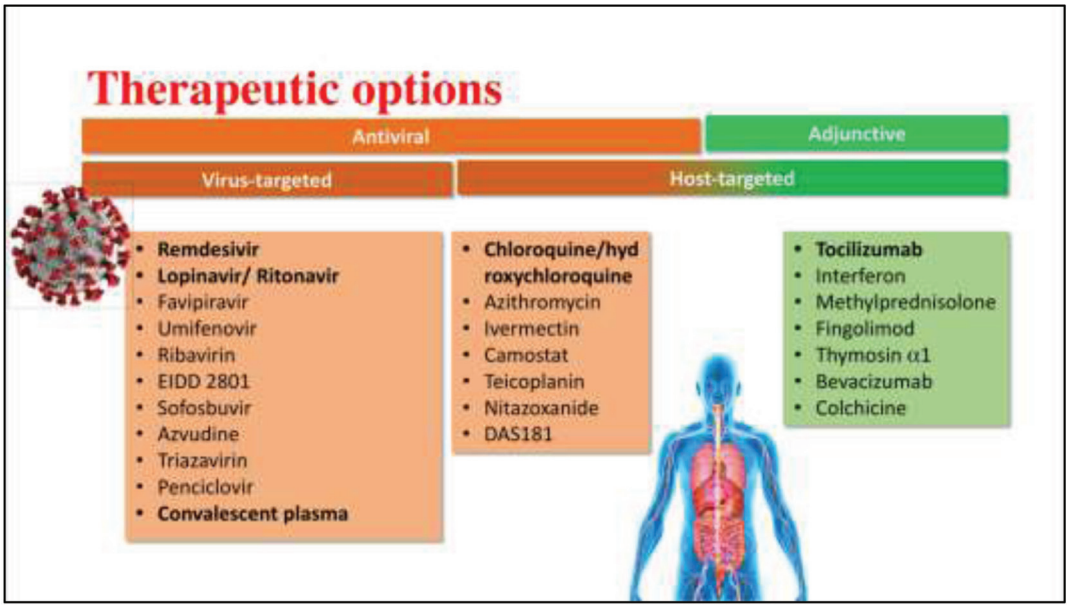
Remdesivir is a novel nucleotide analog product (code GS-5734, Gilead). It has a broad-spectrum antiviral activity against filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses.[27(p)] Remdesivir was first introduced as a therapeutic option against Ebola virus and was shown to reduce the severity of Ebola in human patients.[28] Several studies confirmed a therapeutic and prophylactic activity against MERS-CoV and SARS-CoV in vitro[29] and in vivo.[30,31]

In a lethal murine model of MERS, remdesivir was superior to a regimen of combined interferon beta and lopinavir/ritonavir.[32] In a study on SARS-CoV-2 infected rhesus macaques, early treatment with remdesivir was shown to be beneficial.[31] In COVID-19, the role of remdesivir has been evaluated in a number of observational and randomized controlled trials. All the following studies adopted a regimen of 200 mg of remdesivir on day 1 followed by 100 mg on days 2-10 in single daily infusions. Recently, a RCT found that a 5-day regimen showed similar clinical befinits to a prolonged 10-day course.[33]

The Grein et. Al. study[34] showed that compassionate use of remdesivir led to clinical improvements in 68% of hospitalized patients with severe COVID-19. Adverse Events (AE) included increased levels of hepatic enzymes, diarrhea, rashes, renal impairment, and hypotension, and were more common in patients receiving invasive ventilation. Multiple organ dysfunction syndrome, septic shock, acute kidney injury, and hypotension were the most commonly reported AEs in patients who were receiving invasive ventilation at baseline (23% of patients). Four patients discontinued treatment due to severe side effects.

The Wang et al. study[35]—a randomized, double-blind, placebo-controlled, multicenter trial at ten hospitals—evaluated the use of remdesivir in 237 hospitalized adult COVID-19 patients (158 on remdesivir and 79 on placebo). Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. The study found that remdesivir use was not associated with a difference in time to clinical improvement. AEs were reported in 66% of remdesivir recipients versus 64% of placebo recipients and included constipation, hypoalbuminaemia, hypokalaemia, anemia,

Fig. 1
The therapeutic options currently available against COVID-19 and their classification



thrombocytopenia, and increased total bilirubin. This study was terminated early due to lack of patients, however, so the sample size may have affected the outcome.

Probably the most important treatment study to date on remdesivir role in COVID-19 is the NIH-conducted Adaptive COVID-19 Treatment Trial (ACTT-1)[36] a double-blind, randomized, placebo-controlled trial. Patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p<0.001$). Median time to recovery was 11 days for patients treated with remdesivir compared to 15 days for those who received placebo. This study also demonstrated a survival benefit with a mortality rate of 7.1 % for the group receiving remdesivir versus 11.9% for the placebo group.

A phase 3 SIMPLE trial by Gilead[33] showed that patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course. Time to clinical improvement for 50% of patients was 10 days in the 5-day treatment group & 11 days in the 10-day treatment group. No new safety signals were identified with remdesivir across either treatment groups. Early treatment during the first 10 days of illness was associated with better outcomes (discharge rate 62% vs 49%).

Chloroquine and Hydroxychloroquine

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are established anti-malarial drugs. HCQ is also used for the treatment of rheumatologic disorders. They work by blocking viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. They could also exert immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells after viral infection.[37-39] Several studies examined the role of these agents in the management of COVID-19. Preliminary data from more than 100 patients recruited in clinical trials in China showed that CQ was superior to control in ameliorating the symptoms, diminishing the duration of the disease, and achieving total recovery in patients with COVID-19-associated pneumonia.[40] An open-label non-randomized study (Gautret et al. 2020) included HCQ treatment recipients and patients who refused treatment as a control group. Azithromycin (AZT) was added to the HCQ treatment depending on the clinical situation. In this study, 16.7% of subjects were asymptomatic, 61.1% had upper respiratory tract infection symptoms, and 22.2% had lower respiratory tract infection symptoms. Enhanced viral clearance in HCQ (70%) versus control (12.5%) was identified and the outcomes were even better when azithromycin was added to the regimen (100%).[41] However, this study had several limitations such as a small sample size of 20 patients and the non-randomized early cessation of treatment in 6 HCQ patients. Nevertheless, in a following uncontrolled, non-comparative, observational study, the same group of researchers reported on their experience with 80 relatively mild cases of infected inpatients treated with HCQ/AZT and all except one patient recovered. Nasopharyngeal viral clearance was observed in 83% of the patients by day 7, and 93% by day 8.[42]

Another randomized clinical trial from China examined the use of HCQ (Chen et al. 2020) in 62 hospitalized COVID-19 patients. 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment: TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group (80.6% vs 54.8% Ctrl). On the other hand, an open label randomized controlled trial on HCQ (Tang et al. 2020) in patients with mainly mild to moderate COVID-19. 75 HCQ/ 75 SOC 1200 mg daily for 3 days followed by a maintenance dose of 800 mg daily 2-3 weeks. HCQ did not result in a significantly higher probability of negative conversion (85.4% vs 81.3% in SOC) or time-to-alleviation of symptoms.

A comparative observational study (Mahévas et al. 2020) evaluated 181 adult COVID-19 patients requiring oxygen but not ICU admission who received HCQ 600 mg daily within 48 hours of admission (n=84) versus the standard of care (SOC) (n=89). There was no difference in survival rate, intensive care admissions, or oxygen weaning on day 21.[43]

A prospective randomized study (Chen et al. 2020) of 30 patients with COVID-19 who were given concomitant antivirals found that there was no difference in virologic

outcomes between HCQ (400 mg, daily for 5 days with SOC) and SOC alone.[44] Another observational study (Geleris et al., 2020) also did not show a significant association between HCQ use and intubation or death. It is worth mentioning that HCQ-treated patients were more severely ill at baseline.[45]

The most important study to date is the retrospective study of HCQ & HCQ/AZT at the Veterans Health Administration (Magagnoli et al. 2020) where 368 patients were evaluated (HCQ, n=97; HC+AZT, n=113; no HCQ, n=158) and HCQ was associated with a higher risk of death and the risk of ventilation was similar to that of the control group. However, this study was criticized for patients receiving treatment had more severe disease at baseline.[46]

The Lancet published a controversial multinational registry analysis of the use of HCQ & HCQ/AZT (Mehra et al. 2020) that reported on the results of 96,032 hospitalized COVID-19 patients from 671 hospitals. 14,888 were in the CQ/HCQ treatment group. After several authorities published letters to the Lancet, the journal published an expression of concern regarding this study citing several errors and gaps in the data collection and demanding that the research group provide it with raw data. The study indicates CQ/HCQ use was not associated with benefit but linked to decreased in-hospital survival and increased frequency of ventricular arrhythmias. The researchers also stated that both agents can cause rare and serious adverse effects (<10%), including QTc prolongation (to >500 ms in 23% of patients treated with HCQ/AZT), hypoglycemia, neuropsychiatric effects, and retinopathy. Baseline electrocardiography to evaluate for prolonged QTc is advisable prior to and following initiation of these medications. More recently, scientists in the UK announced stopping the HCQ arm of the RECOVERY trial citing lack of benefit as the cause.[47] However, the data that led to this decisision has not been published yet.

Lopinavir/Ritonavir (LPV/r)

This is a well-known treatment of HIV/AIDS and is listed in the WHO list of essential medicines. This is a combination of two protease inhibitors that showed some efficacy in the treatment of MERS-CoV and SARS-CoV as its use was associated with reduced mortality in the non-human primate model of MERS-CoV. A combination of lopinavir/ritonavir and interferon-β1b (IFN-β1b) was shown to be effective against MERS-CoV in vitro.[32] In addition, lopinavir/ritonavir (500 mg BID for 14 days) in combination with ribavirin (21 days) showed reduced fatality rate and milder disease course during an open clinical trial in patients in the 2003 SARS outbreak.[48]

Regarding its role in the treatment of COVID-19, a randomized, controlled, open-label trial (Cao et al. N Engl J Med 2020) included 199 hospitalized adult COVID-19 patients who received LPV/r (400 mg/100 mg) BID for 14 days plus SOC or SOC alone. The study showed no difference in time to clinical improvement, mortality at day 28, and viral clearance.[49] The population studied was likely severely ill given the high CFR (22.1%) and the fact that 14% of the treatment arm was unable to complete the full 14-day LPV/r course. A large multicenter, open-label, randomized, phase 2 trial (Hung et al. 2020) studied 127 adult COVID-19 patients who received LPV/r treatment within 5 days (IQR 3–7) of illness onset. The combination group received LPV/r 400 mg/100 mg BID, ribavirin 400 mg BID, and 3 doses of 8 million IU IFN-beta-1b on alternate days (N=86). The control group received LPV/r 400 mg/100 mg BID. This study showed that the triple therapy significantly shortened duration of virus shedding compared to the control (7 days [IQR 5–11]) versus (12 days [8–15]; hazard ratio 4·37 [95% CI 1·86–10·24], p=0·0010). Triple therapy also shortened the median hospital stay in the combination group compared to the control group (9·0 days [7·0–13·0] versus 14·5 days [9·3–16·0]; HR 2·72 [1·2–6·13], p=0·016). Nevertheless, this study could not dissect the role of each drug in the observed outcomes. Adverse events included self-limited nausea, fever, diarrhea, & raised alanine transaminase.[50]

Tocilizumab

Tocilizumab (TCZ) is a recombinant anti-human interleukin-6 receptor (IL-6R) monoclonal antibody indicated for the treatment of rheumatoid arthritis. It was approved by the US FDA for the treatment of cytokine release syndrome.

In a retrospective analysis of severe or critical COVID-19 patients treated with TCZ (Xu et al. 2020), within 24 hours of initiating TCZ therapy (4–8 mg/kg body weight), fevers and elevated C-reactive protein levels resolved and IL-6 levels declined. At day 5 of treatment, 75% (15/20) of patients had lowered oxygen intake, lesion opacity had improved by 90.5%, and lymphocytes in peripheral blood had returned to normal in 52.6% of patients (10/19). This study did not report any significant AEs.[51]

In another retrospective review of severe COVID-19 patients (Alattar et al. 2020), TCZ resulted in decline of inflammatory markers, radiological improvement, and reduced ventilatory support requirements. Similar findings were reported by the National Health Commission in China and by Luo et. Al. In France, a study conducted by the *Assistance Publique-Hôpitaux de Paris* comparing SOC only to SOC+TCZ treatment also reported significantly lower proportion of patients in the TCZ arm who died or required ventilation compared to the standard care arm.[52] More recently, Italian researchers shared their experience with TCZ in 100 patients with severe COVID-19 admitted to hospitals in Brescia, the epicenter of Northern Italy. TCZ treatment correlated to reduced levels of CRP, ferritin, and fibrinogen in the serum that were closer to the normal range. In addition, lymphocyte counts and IL-6 serum levels increased. Benefits were rapid and sustained and eventually allowed for extubation and discharge.[53]

Convalescent plasma

Convalescent plasma (CP) is a therapeutic option used in multiple infectious diseases like influenza, Ebola, measles, and SARS.[54] Two small-case series reported improvement in oxygenation, sequentially organ failure assessment (SOFA) scores, and eventual ventilator weaning in patients with severe COVID-19. One dose (200 mL) of CP was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level, leading to the disappearance of viremia in 7 days.[55] Timelines of improvement varied from days to weeks. A retrospectively controlled study in Mount Sinai Hospital showed improved oxygen requirements at day 14.[55] The largest study to date on the use of CP came from the US. The study showed the by day 14 post-transfusion, 76% (19 out of 25) of the patients improved upon treatment and 11 were discharged from the hospital. The authors concluded that CP was well tolerated.

Nevertheless, convalescent plasma therapy still comes with potential theoritical risks such as blood-borne pathogens, transfusion-related acute lung injury (TRALI) in which transferred antibodies damage pulmonary blood vessels, or transfusion-associated circulatory overload (TACO)[56]—both leading to difficulty breathing.[57] Fortunately, though, a recent study by Houstoun Methodists hospitals that treated COVID-19 patients with convalescent plasma, the United States' first safety tiral of convalescent plasma use for SARS-CoV-2 infection treatment, did not report any adverse events and by day 14, 76% of patients had significantly improved, and 44% were discharged.[58] A recent press release by Mount Sinai also documented improved outcomes associated following the transfusion of convalescent plasma with anti-spike antibody titers superior to a dilution of 1:320 and matched to the patient's blood type.[59]

Conclusion

There are many safety and efficacy concerns around chloroquine and hydroxychloroquine which makes remdesivir the currently leading therapeutic option for COVID-19—but doses are limited. This is why large randomized controlled trials should be done to establish the effectiveness of other medications. Solidarity (by the WHO) and Recovery trials (by the UK) should provide important data about potential treatment options. In addition, the lag time between disease onset and start of treatment is a barrier to the efficacy of available therapeutics and patient recovery. On the other hand, tocilizumab and convalescent plasma use seem promising options for the treatment of severe cases of COVID-19. The standard of care remains key in COVID-19 management in addition to remdisivir in the countries where it is available.

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