REVIEW OF THERAPEUTICS

Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019

Ashley Barlow,[1] Kaitlin M. Landolf,[1] Brooke Barlow,[2] Siu Yan Amy Yeung,[1] Jason J. Heavner,[3] Cassidy W. Claassen,[4] and Mojdeh S. Heavner[5]*

[1]Department of Pharmacy, University of Maryland Medical Center, Baltimore, Maryland; [2]Department of Pharmacy, University of Kentucky Healthcare, Lexington, Kentucky; [3]University of Maryland Baltimore Washington Medical Center, Glen Burnie, Maryland; [4]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, Maryland; [5]Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, Maryland

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into an emergent global pandemic. Coronavirus disease 2019 (COVID-19) can manifest on a spectrum of illness from mild disease to severe respiratory failure requiring intensive care unit admission. As the incidence continues to rise at a rapid pace, critical care teams are faced with challenging treatment decisions. There is currently no widely accepted standard of care in the pharmacologic management of patients with COVID-19. Urgent identification of potential treatment strategies is a priority. Therapies include novel agents available in clinical trials or through compassionate use, and other drugs, repurposed antiviral and immunomodulating therapies. Many have demonstrated in vitro or in vivo potential against other viruses that are similar to SARS-CoV-2. Critically ill patients with COVID-19 have additional considerations related to adjustments for organ impairment and renal replacement therapies, complex lists of concurrent medications, limitations with drug administration and compatibility, and unique toxicities that should be evaluated when utilizing these therapies. The purpose of this review is to summarize practical considerations for pharmacotherapy in patients with COVID-19, with the intent of serving as a resource for health care providers at the forefront of clinical care during this pandemic.
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The recent outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and subsequent coronavirus disease 2019 (COVID-19) has created a global health emergency with unparalleled worldwide burden.[1] The full epidemiological impact of this virus remains to be seen, but an understanding of the approximate denominator will be important when considering the clinical characteristics of these cases and the percentage of cases with more severe disease or resultant mortality.[2] In December 2019, the first reports of COVID-19 included a cluster of patients hospitalized with pneumonia in Wuhan, China. The most common presenting symptoms in these patients were fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%).[3] Characteristic laboratory and radiologic findings included lymphopenia (63%) and rapid development of multiple patchy consolidations and ground glass opacities bilaterally with a notable peripheral distribution seen on chest

computed tomography (CT).[3, 4] Patients may present with a chest CT suggestive of COVID-19 even before developing a positive reverse transcription-polymerase chain reaction assay result.[5]

Epidemiology and diagnostics for COVID-19 are rapidly evolving, giving us greater understanding of those at risk and elucidating more potential pharmacologic targets.[6] SARS-CoV-2 is a betacoronavirus, in the same subgroup as severe acute respiratory syndrome-coronavirus (SARS-CoV) that caused the SARS outbreak in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) that caused the MERS outbreak in 2012.[7] As such, a rational approach to initial therapies to target COVID-19 would be those that were studied during the SARS and MERS outbreaks. Novel therapies and repurposing of old drugs are now being studied as therapeutic strategies against COVID-19.

Treatment strategies that have been identified thus far include medications uncommonly used in clinical practice. Our understanding of important practical considerations is quite limited. In one study, ~25% of patients with COVID-19 required admission to an intensive care unit (ICU). These patients were older (66 vs 51 yrs of age) and more likely to have underlying comorbidities (72% vs 37%).[8] A study in Wuhan showed that of 52 critically ill ICU patients infected with SARS-CoV-2, mortality was 61.5%; among all ICU patients with COVID-19, organ dysfunction included acute respiratory distress syndrome (ARDS) (67%), acute kidney injury (29%), and hepatic dysfunction (29%).[9] In the ICU, the level of complexity required in the care of these patients involves the underlying disease state(s), multitudes of comorbidities, and polypharmacy.

The intent of this review is to provide health care providers with foundational knowledge on the therapies that have been proposed for use against COVID-19. We review critical key concepts for consideration in the use of these therapies in practice, particularly in the ICU setting where the most severe patients will be managed.

Pharmacologic Targets for COVID-19

Pharmacologic therapies against SARS-CoV-2 target its viral structure and genome (Figure 1). SARS-CoV-2 expresses viral proteins on its outer surface that facilitate attachment on to host cells via angiotensin-converting enzyme 2 (ACE2). SARS-CoV-2 is a single-stranded ribonucleic acid (RNA) beta coronavirus that replicates by recruiting nonstructural proteins such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase.[10] These structural components have some similarities to other known viruses such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), prompting repurposing of currently approved antiviral therapies targeted at these viruses. Nucleoside analogs available for HIV and respiratory viruses may have a therapeutic role in blocking RNA synthesis by targeting the RNA-dependent RNA polymerase found in SARS-CoV-2. Furthermore, the currently available HIV protease inhibitors have displayed some in vitro activity against the 3-chymotryspin-like protease found in SARS and MERS.[10]

It is critical to be aware that currently available therapies have been specifically designed to target the viral genome of a certain virus, and the SARS-CoV-2 physical structure may differ, limiting in vivo efficacy.[10] Other nonstructural or accessory proteins have a role for potential therapeutic targets in development as shown in Figure 1. As opposed to directly targeting viral replication, other therapeutic approaches can be aimed at modulating the innate immune system to attack the virus or inhibit cytokines that are upregulated during viral replication to dampen the physiologic response to disease.[11, 12] Practical considerations for current therapies available against SARS-CoV-2 are summarized in Tables 1 and 2 and discussed at length in the following sections.

Antiviral Therapeutics

Remdesivir

Therapeutic Uses

Remdesivir (GS-5734) is an investigational antiviral agent undergoing phase 3 clinical trials for the treatment of COVID-19. Remdesivir was initially developed for the treatment of Ebola hemorrhagic fever with trials still ongoing; however, it has not been approved globally for any indication.[13] In vitro and in vivo animal data suggest activity against paramyxoviridae, filoviridae, and the coronaviridae including MERS-CoV, SARS-CoV, and SARS-CoV-2.[3, 14–16]

Mechanism of Action

Remdesivir is a 1′-cyano-substituted adenosine nucleotide analog.[17] As a prodrug, remdesivir is
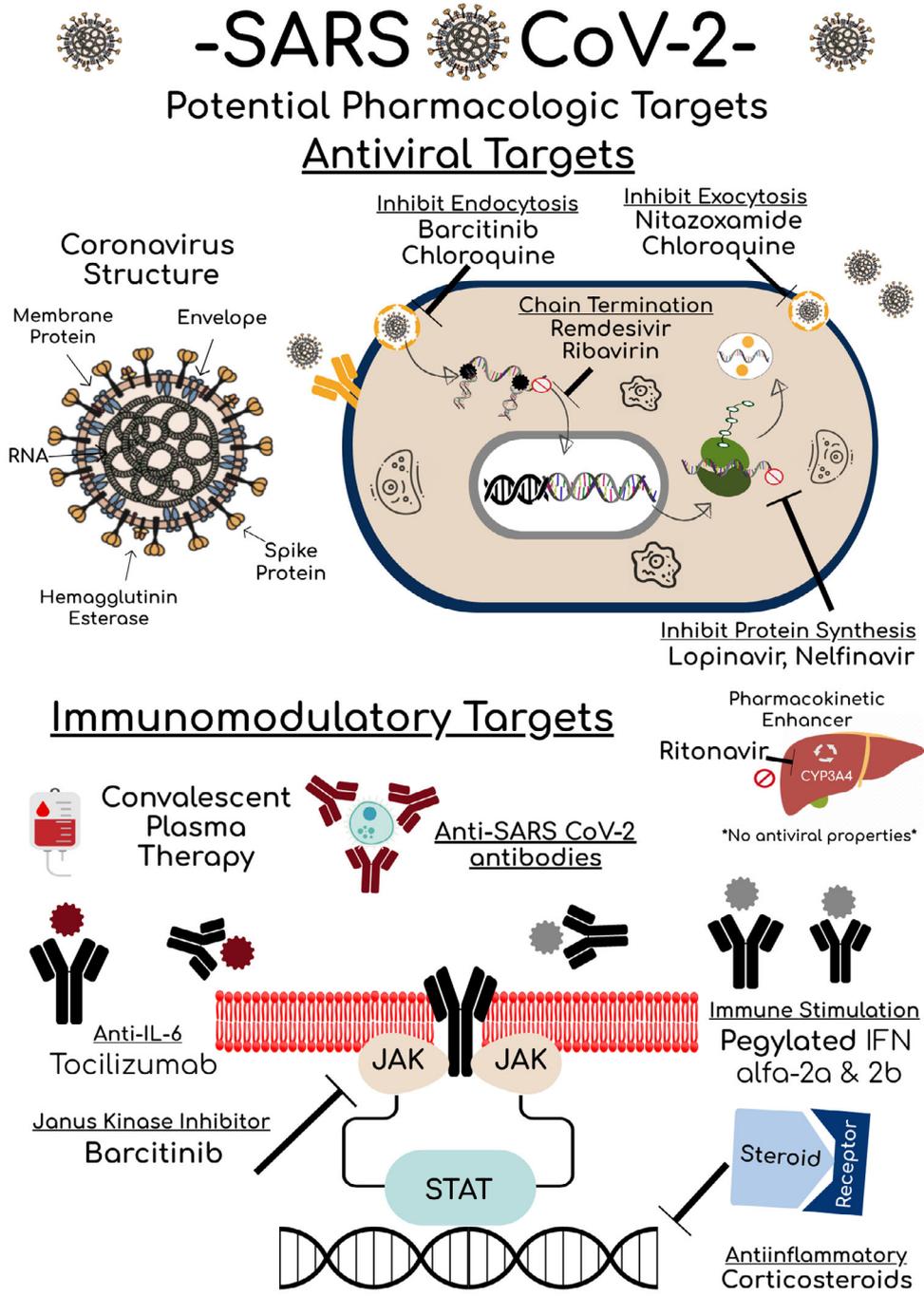
Figure 1. SARS-CoV-2 Potential Pharmacologic Targets. COVID = coronavirus; CYP3A4 = cytochrome 3A4; JAK = Janus kinase; IFN = interferon; IL-6 = interleukin 6; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; STAT = signal transducer and activator proteins.

metabolized in cells and tissues to an active nucleoside triphosphate (GS-443902) that inhibits viral RNA-dependent RNA polymerases early in the viral infectious cycle.[18, 19] Other potential mechanisms of this adenosine nucleotide analog may involve lethal mutagenesis and chain termination.[18] The incorporation of active

nucleoside triphosphate via remdesivir at the beginning stages of replication of murine hepatitis virus in vitro had the most profound effect at 2 hours pre- and postinfection with a decreasing effect greater than 4 hours postinfection, suggesting a time-dependent effect for drug activity.[18]

Table 1. Practical Considerations of Antiviral Therapies Proposed against Severe Acute Respiratory Syndrome Coronavirus 2

Drug	Remdesivir[21, 22, 35]	Chloroquine[39]	Hydroxychloroquine[33, 40]	LPV/r[44, 55, 93]	Ribavirin[59]	Nitazoxanide[68]	Nelfinavir[82]
Dosing	200 mg IV on day 1, then 100 mg IV/day for 5–10 days	500 mg by mouth twice/day for 10 days	400 mg by mouth twice/day for 1 day, then 200 mg twice/day for 4 days	400 mg/100 mg by mouth twice/day for 14 days	*Not established* In clinical trials, 400 mg by mouth twice/day for 14 days	500 mg by mouth twice/day *Duration not defined*	Not studied in humans for SARS-CoV-2
Formulation	IV contains β-cyclodextrin	Oral tablet, oral solution contains propylene glycol	Oral tablet	Oral tablet, oral solution contains ethanol 42.4%[a] and propylene glycol	Oral tablet, oral solution contains propylene glycol, inhaled, IV not available in United States	Controlled-release tablet, oral suspension Formulations are not bioequivalent	Oral tablet
Administration	IV over 30 min	Administer with food Can be crushed Consider diluting when used in a feeding tube	Administer with food Do not crush Film coating must be removed to before compounding	Administer with or without food Do not crush tablets Do not dilute solution (risk of precipitation), administer solution down a feeding tube with milk (no water) Solution incompatible with polyurethane feeding tubes	Administer with food Do not crush (hazardous) PPE must be worn during administration with all dosage forms	Administer with or without food Can be crushed and mixed with food Reconstituted powder stable for 7 days	Administer with food Can be crushed Avoid mixing with acidic foods
Dose adjustments	Renal: Cl_{cr} < 30 ml/min: Not studied RRT: Not studied Hepatic: Not studied	Renal: N/A RRT: HD = 50% dose reduction CRRT = full dose Hepatic: N/A, use with caution	Renal: N/A RRT: N/A, use with caution Hepatic: N/A, use with caution	Renal: N/A RRT: Avoid against once/day dosing Hepatic: Caution in severe liver impairment	Renal: Cl_{cr} 30–50 ml/min: 50% reduction Cl_{cr} < 30 ml/min 75% reduction RRT: Not established Hepatic: Child-Pugh class B and C not recommended	Renal: N/A RRT: No data Hepatic: N/A	Renal: N/A RRT: N/A Hepatic: Child-Pugh class B and C not recommended
Drug interactions	None identified; metabolized to active form via intracellular kinase	Avoid CYP2D6 inhibitors or inducers Avoid use with LPV/r Avoid antacids within 4 hrs of a dose Caution use with medications that increase QTc or cause hypoglycemia		Avoid CYP3A4, P-gp, OATP1B1, OATP1B3, and UGT substrates	No Interactions	No interactions	Avoid CYP3A4 and CYP2C19 inducers or inhibitors

(continued)

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Drug	Remdesivir[21, 22, 35]	Chloroquine[39]	Hydroxychloroquine[33, 40]	LPV/r[44, 55, 93]	Ribavirin[59]	Nitazoxanide[68]	Nelfinavir[82]
Side effects	Data limited, reports of increased LFTs, nausea, vomiting, gastroparesis, rectal bleeding hypomagnesemia, nausea, dry cough, rashes, teratogenic	Nausea, vomiting, abdominal cramping, metallic taste, hemolysis (G6PD deficient), QTc prolongation, skin eruptions	Abdominal pain, nausea, headache, urine discoloration, diarrhea, dizziness, urticaria	Diarrhea, nausea, vomiting, increased serum amylase and LFTs	Hemolytic anemia, hypocalcemia,	Diarrhea, nausea, flatulence, increase LFTs	

Cl_{cr} = creatinine clearance; CRRT = continuous renal replacement therapy; CYP = cytochrome P450; G6PD = glucose-6-phosphate-dehydrogenase deficiency; HD = hemodialysis; IV = intravenous; LFTs = liver function tests; LPV/r = lopinavir/ritonavir; N/A = no adjustment; OATP = organic anion transporting polypeptide; P-gp = P-glycoprotein; PPE = personal protective equipment; RRT = renal replacement therapy; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; UGT = UDP-glucuronosyltransferase.
aDisulfiram-like reactions may occur with disulfiram or other drugs that produce these reactions (e.g., metronidazole).

Rationale for Proposed Therapy

Nucleotide analogs are used for viral RNA or DNA polymerase inhibition and have demonstrated decreased viral replication with their use. Resistance to mutagens of other medications in vitro has resulted in exo-ribonuclease proofreading and removal. Remdesivir has shown potential to avoid this proofreading and thus removal via the exo-ribonuclease.[18] In vitro studies in human airway epithelial cell cultures as a lung model have found activity against coronaviruses.[15] Studies assessing the potency of remdesivir were efficacious among divergent coronaviruses in human airway epithelial cells.[18] Based on the existing evidence for remdesivir activity against SARS-CoV and similar viruses, remdesivir is being investigated for its use against SARS-CoV-2. In the United States, remdesivir has been used for compassionate purposes for a duration of 4–10 days. In these patients, remdesivir was continued until improvement in respiratory symptoms.[20]

Dosing and Pharmacokinetics

Ongoing clinical trials are studying remdesivir with a loading dose of 200 mg intravenously followed by 100 mg/day intravenously for 5 to 10 days in adult patients.[21, 22] Dosing for patients weighing less than 40 kg with a 5 mg/kg loading dose followed by a 2.5 mg/kg once/day maintenance dose has been studied for the treatment of Ebola.[23]

The existing remdesivir pharmacokinetic data are extrapolated from in vitro human cell data and in vivo mouse and nonhuman primate data. Remdesivir is converted from the parent metabolite to the active metabolite, a triphosphorylated nucleoside, via anabolic intracellular kinase.[24, 25] Mice received remdesivir subcutaneously as 50 mg/kg once/day or 25 mg/kg twice/day with a decrease in plasma concentrations of the prodrug and a steady concentration of the activated drug in the lung.[15] In the murine model, twice/day dosing maintained lung concentrations for a longer duration. In the in vitro human lung cell model and the in vivo nonhuman primate model, once/day dosing was found to reach sufficient concentrations with remdesivir demonstrating an activated nucleoside triphosphate half-life of ~20 hours.[19, 26]

No data are available to date regarding remdesivir dosing in patients with renal or hepatic impairment. Data on clearance of remdesivir in

renal replacement therapy are also not yet available. Important pharmacokinetic considerations will need to be elucidated, given that patients receiving remdesivir are likely to be critically ill with end-organ failure.[9]

Adverse Effects

Reported adverse effects of remdesivir after use in three patients in the United States included nausea, vomiting, gastroparesis, or rectal bleeding with no other reported symptoms. These patients also experienced elevated aminotransferase levels occurring 1–5 days after initiating remdesivir.[20] However, it is unclear whether this laboratory change is due to the drug itself or the virus because a third of critically ill patients with COVID-19 have been observed with liver dysfunction.[9] In a study using remdesivir for Ebola virus in humans, one patient experienced hypotension during infusion of the loading dose, necessitating discontinuation; that patient ultimately died due to cardiac arrest.[27] A patient experienced neurologic complications after receiving remdesivir for Ebola treatment in a phase 1 study; however, it is not clear if this was due exclusively to having received remdesivir.[19] Currently, the data on remdesivir use in humans are too sparse to have a clear adverse effect profile for this agent. Current phase 3 randomized clinical trials will provide more conclusive insight into the adverse effects of remdesivir.[21, 22, 28]

Administration Considerations

Remdesivir is manufactured as a lyophilized powder that requires reconstitution and is administered intravenously over 30 minutes. The infusion duration has also been extended over longer times to obtain higher intracellular concentrations of the active metabolite.[29] No data are available regarding compatibility of remdesivir with other intravenous medications. To date, drug-drug and drug-nutrition interactions have not been reported.

Chloroquine and Hydroxychloroquine

Therapeutic Uses

Chloroquine analogs, chloroquine phosphate and hydroxychloroquine, have been used for the prevention and treatment of malaria since the early 1900s.[30] Aside from their antimalarial properties, chloroquine analogs possess immunomodulatory effects lending to their utility for the treatment of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis. The multimodal properties of chloroquine analogs and their minimal toxicity profile have led to their investigation in the treatment of virus-induced illness where the pathologic features are driven by an inflammatory response, such as in HIV-associated immune reconstitution inflammatory syndrome.[31]

Mechanism of Action

Chloroquine analogs are weak bases, that, in their non-protonated form, penetrate and concentrate within acidic intracellular organelles such as endosomes and lysosomes. Once present intracellularly, chloroquine analogs become protonated and increase intravesicular pH, resulting in prevention of endosomal trafficking, dysfunctional cellular enzymes, and impaired protein synthesis.[30] Chloroquine-mediated pH alterations have been proposed to result in early inhibition of viral replication through interference with endosome-mediated viral entry or late transport of the enveloped virus. This mechanism has translated to the potential role of chloroquine analogs in the treatment of COVID-19 and also appears to interfere with the terminal glycosylation of ACE2 receptor expression that prevents SARS-CoV-2 receptor binding and subsequent spread of infection.[32]

Rationale for Proposed Therapy

Clinical data supporting the use of chloroquine analogs in the treatment of coronavirus have centered around several in vitro studies from the SARS-CoV outbreak in the early 2000s with the use of chloroquine. One group tested the cytotoxic potential of chloroquine against SARS-CoV in an in vitro cell culture. Chloroquine demonstrated a potent cytotoxic response with a 99% inhibition of viral replication at day 3.[33] Further in vitro models supported its cytotoxic response and observed that application of chloroquine before viral exposure resulted in favorable inhibition of viral spread, suggesting its potential role as an effective prophylactic intervention.[32]

Hydroxychloroquine, a hydroxy derivative of chloroquine with an improved safety profile, has also been studied in vitro against SARS-CoV-2 with a 3-fold higher cytotoxic potential compared

Table 2. Practical Considerations of Immunomodulatory Therapies Proposed against Severe Acute Respiratory Syndrome Coronavirus 2

Drug	Interferon α/β[52, 87]	Baricitinib[98]	Tocilizumab[93, 102, 108]
Dosing	Not established Clinical trial: Interferon-β-1b 0.25 mg subcutaneous injection alternate day for 3 days	Not studied in humans	4–8 mg/kg IV once (maximum 800 mg) *or* 400 mg IV once dose Consider additional dose 8–12 hrs later if continued clinical decompensation (maximum total dose of 2 doses)
Formulation	Subcutaneous injection Formulations studied[a]: alpha-2b, beta-1b	Oral tablet	IV
Administration	Injection can be performed into the abdomen or thigh Rotate injection sites	Without regard to meals No data for compounding, may be hazardous (carcinogenic)	IV infusion over 1 hr
Dose adjustments	Renal: Cl_{cr} < 30 ml/min[b] RRT: Not established, may experience increased adverse effects Hepatic: Child-Pugh class B and C not recommended	Renal: eGFR 30–60 ml/min/1.73 m^2 decrease to 1 mg/day[c] Cl_{cr} < 30 ml/min: Avoid RRT: N/A Hepatic: Caution in severe liver impairment	Renal: N/A RRT: N/A Hepatic: Hold if LFTs 1-3 × ULN (may resume when LFTs normalize)
Drug interactions	N/A	Avoid strong OAT 3 inhibitors	Moderate induction of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, may decrease concentration of substrates
Side effects	Flulike symptoms (fever, myalgias, and headaches), leukopenia, lymphopenia, depression, injection site pain, autoimmune hepatitis, and thyroiditis	Boxed warnings: Infection, upper respiratory tract infection, malignancy, thrombosis Other: Neutropenia, elevations in platelets, LFTs, lipids, creatinine, and creatinine phosphokinase	Infusion reactions, infection, neutropenia, thrombocytopenia, increased liver enzymes, and lipid abnormalities

Cl_{cr} = creatinine clearance; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate; IV = intravenous; LFTs = liver function tests; N/A = no adjustment; OAT = organic anion transporting; RRT = renal replacement therapy; ULN = upper limit of normal.
[a]Inhaled studied; formulation not available in United States.
[b]Pegylated formulation only.
[c]Based on dose adjustments for rheumatoid arthritis.

with chloroquine.[34] One study demonstrated potent antiviral effect at both entry and post-entry states at plasma concentrations of 6.90 μM. This concentration can be safely achieved in humans.[35] Clinical data in humans thus far have been limited, with the best available evidence to date from more than 100 patients from 10 different hospitals in China during the current COVID-19 outbreak. This pooled analysis demonstrated superiority of chloroquine compared with control in inhibiting exacerbations of pneumonia, improving lung imaging findings, promoting viral negative conversion, and shortening the disease course in the absence of any adverse effects.[36] The dual mechanism of antiviral and antiinflammatory effects of chloroquine were proposed to account for its utility in preventing COVID-19–related pneumonia. Ongoing trials for hydroxychloroquine are actively recruiting with hopes to further delineate its role in the treatment paradigm for COVID-19.[37]

Dosing and Pharmacokinetics

Chloroquine is formulated as a tablet in a phosphate salt form for oral administration. In the treatment of COVID-19, expert consensus recommends a chloroquine phosphate tablet at a dose of 500 mg orally twice/day for a duration of 10 days.[38] Bioavailability after oral administration is complete (~60–100%) and rapid within 30 minutes. Chloroquine is widely distributed into nearly every organ system including the eyes, heart, kidney, liver, and lungs where retention is prolonged.[39] Chloroquine is metabolized into an active metabolite, desethyl chloroquine, via hepatic enzymes cytochrome P450 (CYP) 2C8 and CYP3A4. This metabolite accounts for

a small portion of its pharmacologic activity. Chloroquine is a major substrate of CYP2D6. This enzyme accounts for ~30% of its inactivation; inhibitors of this enzyme should be avoided due to a heightened risk of accumulation and toxicity. Chloroquine is predominantly eliminated in the urine with ~50% of a dose recovered unchanged. No dose adjustments are needed if creatinine clearance (Cl_{cr}) is above 10 ml/minute; however, administration of 50% of the dose is required in patients on intermittent hemodialysis, peritoneal dialysis, or if Cl_{cr} is below 10 ml/minute. Patients receiving continuous renal replacement therapy (CRRT) should receive full-dose chloroquine.[39]

Hydroxychloroquine sulfate is available as a film-coated tablet for oral administration. Dosing recommendations for COVID-19 are not well-defined, and clinical trials and in vitro data are ongoing to assist with dose optimization. Current in vitro pharmacokinetic models suggest a loading dose of hydroxychloroquine 400 mg orally twice/day on day 1, followed by 200 mg orally twice/day for 4 days. Hydroxychloroquine has similar or possibly superior cytotoxic effects against SARS-CoV-2 as chloroquine 500 mg twice/day. Translation of the cytotoxic effects of hydroxychloroquine in vivo remains unknown.[34] A clinical trial of hydroxychloroquine for COVID-19 is actively recruiting, with a planned intervention of 400 mg by mouth once/day for a total duration of 5 days.[37] The major difference in dosing strategies is the utility of a loading dose. Given that the terminal half-life of hydroxychloroquine is ~50 days in blood and remains in the body for up to 3 months, a loading dose is a reasonable approach until the clinical outcomes from ongoing trials are published. Hydroxychloroquine has rapid absorption after oral administration, a wide volume of distribution (Vd), and prolonged half-life. Metabolism and elimination of hydroxychloroquine differ from chloroquine because reliance on CYP enzymes for elimination is minimal and clearance is not correlated with renal function. No renal or hepatic dose adjustments are recommended; however, cautious use with severe impairment is advised. Given the wide Vd (~15.5 L/hr) and high lipophilicity of the compound, CRRT is likely to have minimal impact on drug removal.

Adverse Effects

Chloroquine and hydroxychloroquine are generally well tolerated. The most common adverse effects are gastrointestinal intolerances such as nausea, vomiting, abdominal cramping, and a metallic taste. Acute toxicity in the setting of supratherapeutic dosing may manifest as cardiomyopathy, neuropathy, or myopathy. Retinopathy, a hallmark toxicity of hydroxychloroquine and chloroquine, is predominantly associated with high doses, long-term administration (i.e., hydroxychloroquine for systemic lupus erythematosus or rheumatoid arthritis), and are unlikely of concern in the setting of COVID-19 treatment. Although the manufacturer's labeling of chloroquine and hydroxychloroquine cautions against their use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, only limited data support this risk, and no incidence of hemolytic anemia was seen in patients with G6PD in 30 years of drug exposure.[39, 40] Both agents are safe in pregnancy with minimal risk of congenital malformations.[41] Albeit rare, use in patients with preexisting cardiac disease or QTc prolongation should be avoided due to the risk of torsades de pointes.

Concurrent administration of QTc prolonging agents and strong 2D6 inhibitors (chloroquine only) should be avoided to minimize cardiac adverse effects. Notable dermatologic adverse effects can include photosensitivity, lichenoid reactions, and drug eruptions with chloroquine, and acute generalized exanthematous pustulosis with hydroxychloroquine.[39, 40] In postmarketing data, case reports of hypoglycemia progressing to loss of consciousness occurred with these agents in patients with a history of diabetes on concurrent antidiabetic agents.[39, 40] The proposed mechanism of hypoglycemia involves inhibited insulin degradation. Patients have required up to a 30% reduction in insulin doses with concurrent hydroxychloroquine administration.[42] Baseline and routine monitoring of blood glucose and electrocardiogram for the QTc interval are recommended for patients on chloroquine analog therapy.

Administration Considerations

To mitigate nausea and vomiting, it is recommended to administer chloroquine and hydroxychloroquine with food. Chloroquine can be crushed and mixed with flavored syrups or enclosed in gelatin capsules to mask the bitter taste.[39] In patients who are mechanically ventilated, chloroquine can be extemporaneously compounded into oral suspension. Hydroxychloroquine tablets should not be crushed or split at the bedside for administration but

instead require removal of the film coating to be compounded extemporaneously into a solution for administration via enteral tubes. Neither agent is available for intravenous administration and would be an unfavorable option in patients who are not permitted to take anything by mouth or have no enteral access.

Administration of antacids within 4 hours of chloroquine should be avoided due to a potential for chelation and reduced bioavailability. This interaction is not present with hydroxychloroquine. A theoretical drug-drug interaction exists between proton pump inhibitors (PPIs) and chloroquine analogs because the blockage of H+, K+ −ATPase by PPIs in lysosomes can raise the pH and reduce drug accumulation that could weaken immunomodulatory effects. However, effects of this interaction in vivo are unknown.[39, 40]

Lopinavir/Ritonavir

Therapeutic Uses

Lopinavir (LPV) is an aspartic acid protease inhibitor developed for the treatment of HIV. Lopinavir is co-formulated with ritonavir (LPV/r) to boost the pharmacokinetic activity and half-life of LPV through inhibition of CYP450. LPV/r provides potent and sustained viral load reductions for patients with HIV, which has prompted interest in assessing its efficacy in other viruses that function with similar machinery.[43]

Mechanism of Action

Proteases are essential enzymes for the production and maturation of viral genomes. The primary antiviral effect of protease inhibitors is prevention of viral replication, thus limiting spread into host cells.[43] The therapeutic rationale for LPV/r arises from in vitro studies demonstrating inhibition of the 3-chymotrypsin-like protease found in novel coronaviruses.[44, 45] However, LPV was specifically designed to match the structure of the C2 catalytic site within the HIV aspartic acid protease. SARS-CoV-2 protease is a cysteine protease family and structurally dissimilar because it lacks a C2 catalytic site.[10]

Rationale for Proposed Therapy

The therapeutic value of LPV/r emerged from in vitro studies testing its utility for SARS and MERS. In vitro testing of LPV/r was performed for severe MERS-CoV in marmosets. Lopinavir/ritonavir improved clinical scores for weight loss and symptom burden, improved radiologic clearance, and decreased viral loads in necroscopied lungs.[45] The benefit of LPV/r has yet to be clearly replicated in human cell cultures, with some studies showing complete lack of in vitro activity.[46] Clinical in vivo studies from SARS and MERS outbreaks demonstrated that the use of LPV/r 400–100 mg by mouth twice/day combined with ribavirin with or without corticosteroids initiated during the early phase of viral acquisition reduced rates of ARDS or death when compared with a matched cohort that received supportive care or ribavirin alone.[44, 47, 48] However, these findings did not remain significant if LPV/r was initiated later in the disease course, reiterating the lack of pharmacologic effect against a viral genome that has been integrated into host DNA.[48]

Available literature to date for LPV/r in the treatment of COVID-19 stems from a descriptive case series of five patients in Singapore receiving LPV/r 200–100 mg twice/day for 14 days. Three patients had reductions in ventilation requirements within 3 days of treatment initiation, but two had progressive respiratory failure. Despite the lower dosing regimen compared with previous studies, four of the five patients had premature treatment discontinuation secondary to nausea, vomiting, diarrhea, and increased liver function tests. No deaths occurred in the study, but efficacy outcomes are difficult to interpret based on the lower dosing strategy compared with previous data. This does raise concerns about the potential tolerability of the higher dose regimen.[49]

Another retrospective cohort showed that LPV/r has limited influence on the duration of viral shedding that can occur for a median of 20 days after initially contracting the virus.[49, 50] In a recent randomized controlled open-label trial including hospitalized patients with SARS-CoV-2 infection, patients receiving LPV/r 400−100 mg twice/day for 14 days versus standard of care found no benefit versus standard of care treatment.[51] Multiple ongoing studies have evaluated the clinical utility of LPV/r as monotherapy and in combination with other therapies such as ribavirin and interferon (IFN).[52–54]

Dosing and Pharmacokinetics

Lopinavir/ritonavir is available as a single-tablet formulation (Kaletra) in dosage strengths

of 400/100 mg or 200/100 mg. Given the largest available evidence from in vitro studies, if LPV/r is used as an adjunctive agent for COVID-19, a dose of 400 mg/100 mg by mouth twice/day for 14 days is recommended. The drug is highly protein bound (~98%), and its primary pathway for elimination is through the hepatobiliary system. No dose adjustments are required for renal impairment. In patients receiving intermittent hemodialysis, however, once/day dosing is not recommended when indicated for treatment of HIV. This does not influence use in COVID-19 because the recommended schedule is twice/day.[43] No dosage adjustments are recommended in hepatic impairment, but caution should be advised if used in patients with advanced liver disease.[55] Lower dosages of 200/100 mg twice/day can be considered where adverse effects limit tolerability, with the understanding that lower doses may not substantially mitigate toxicities. Based on information collected by the Antiretroviral Pregnancy Registry, an increased risk of teratogenic effects has not been observed in humans. The Health and Human Services perinatal HIV guidelines consider LPV/r a therapeutic option for pregnant women living with HIV and can be continued if conception occurs during therapy.[56]

The considerable potential for drug-drug interactions with LPV/r requires a thorough review of concomitant medications. Ritonavir is a strong inhibitor of CYP3A4, a major enzyme responsible for the metabolism and elimination of many medications. In addition, ritonavir is a moderate inhibitor of p-glycoprotein (P-gp), organic anion transporter (OATP1B1), OATP1B3, and is an inducer of UDP-glucuronosyltransferase.[55] Patients requiring ICU admission for COVID-19 are often elderly with multiple comorbidities and polypharmacy. The potential therapeutic benefit of LPV/r should be weighed against considerable interactions with commonly used medications in the ICU (e.g., midazolam, fentanyl, antiarrhythmics).[3]

Adverse Effects

Treatment with LPV/r may result in intolerable gastrointestinal toxicities, although administration with food may ameliorate the severity of these symptoms. Up to 24% of patients experience diarrhea, although it usually improves within 2 weeks.[55] Adverse events particularly relevant to ICU patients include potentially fatal pancreatitis, hepatitis, hepatic decompensation among those with preexisting liver disease, and increased PR intervals, especially in those with congenital QTc prolongation.[55]

Previous studies using LPV/r for SARS demonstrated increased serum amylase and liver enzyme elevations compared with a matched cohort. Routine monitoring of liver function tests is critical, and supportive care with antiemetics and antimotility agents should be considered.[44] Cardiovascular and metabolic toxicities such as lipid abnormalities are commonly observed in patients with HIV receiving these therapies for prolonged periods; these are less likely when used for the abbreviated durations for COVID-19.

Administration Considerations

Lopinavir/ritonavir tablets should not be chewed or crushed for patients unable to swallow.[55] In patients who are intubated or have limited oral access, an oral suspension is available for delivery via a nasogastric tube.[55] Of note, the suspension does contain 42.4% ethanol. Available data suggest administration with enteral nutrition does not adversely impact drug concentrations.[57] Coadministration with food that contains a moderate to high fat content can enhance LPV/r bioavailability.[55]

Ribavirin

Therapeutic Uses

Ribavirin is a purine nucleoside analog that elicits its antiviral affect through inhibition of viral RNA synthesis. Ribavirin is a prodrug that undergoes metabolic conversion by the liver, after which its metabolic structure closely mimics the purine analog guanosine that enhances its incorporation into RNA. The structural elements prohibit the subsequent addition of nucleoside analogs, effectively halting the synthesis of RNA.[58] Ribonucleic acid is ubiquitous in many viruses, which is why ribavirin has been studied in a broad range of viral diseases including hepatitis B, C, and respiratory syncytial virus.[59]

Rationale for Proposed Therapy

The nonselective antiviral properties of ribavirin prompted investigators to evaluate its use during the SARS and MERS outbreaks. During the initial SARS outbreak, ribavirin was used throughout Hong Kong in both oral and

intravenous formulations.[60] However, the distribution of the intravenous formulation, which is not available in all countries including the United States, was restricted in the midst of the epidemic given the concern for lack of in vitro susceptibility and considerable toxicity. In 126 patients treated with ribavirin, hemolysis and anemia occurred in up to 76% and 49% of cases, respectively.[61, 62] In vivo data suggest serum concentrations of ribavirin needed to blunt viral replication effectively is higher than what is safely achievable in humans.[61] In vitro data suggest rapid resistance against SARS and MERS when used as a monotherapy but potential activity when combined with other antivirals such as LPV/r or chloroquine analogs.[38, 63] Outcomes for ribavirin use in combination with interferon (IFN)-α-2a for MERS-CoV is discussed in the IFN section.

Dosing and Pharmacokinetics

Ribavirin is commercially available as an oral capsule, oral solution, and inhaled formulation.[59] The inhaled formulation has not been studied for SARS, MERS, or COVID-19, and the intravenous form is not available in the United States. Oral ribavirin has been dosed as a 4-g loading dose followed by 1.2 g every 8 hours in two small studies for SARS.[44, 64] In the management of COVID-19, data are limited to ongoing studies using a dosing strategy of 400 mg by mouth twice/day for 14 days as a part of a combination regimen.

Ribavirin has a prolonged half-life of ~40 days. Loading doses may aid in achieving steady state more rapidly.[65] Ribavirin is metabolized to its active form via extrahepatic enzymes.[59] However, its use in hepatic impairment Child-Pugh class B and C is not recommended given that it is metabolized by CYP enzyme pathways. Ribavirin is eliminated primarily by renal excretion, requiring strict dose reductions for renal insufficiency that varies based on indication.[59] A review on the use of ribavirin in SARS recommended a 50% dose reduction for Cl_{cr} between 30 and 50 ml/minute, and a 75% reduction for Cl of below 30 ml/minute.[65] There is no established safety of ribavirin in patients receiving renal replacement therapy; it should be restricted to those with stable renal function.

Adverse Effects

Ribavirin carries a boxed warning for hemolytic anemia.[59] In a study assessing the adverse effects associated with the use of ribavirin use for SARS, the most common adverse effects were hemolytic anemia (61%), hypocalcemia (58%), and hypomagnesemia (46%).[66] The onset of hemolytic anemia occurs as early as 3–5 days after therapy with high doses (above 1–2 g) that were used as loading doses for coronavirus.[44, 67] The risk is highest in patients who are elderly or have poor renal function, but consideration should also be taken in patients with preexisting cardiac disease where reduction in hemoglobin increases the risk of decompensation.[59] Ribavirin is a teratogen with a significant potential for embryonic toxicity and contraindicated in women who are pregnant and in male partners of women who are pregnant. If ribavirin is considered in women or men of childbearing potential, use of systemic and barrier contraception must be strictly enforced. Because active metabolites of ribavirin persist in plasma for up to 6 months, contraception is required both during treatment and for at least 6 months after treatment is completed.[59]

Ribavirin does not have drug-drug interactions because its metabolism and elimination does not rely on the CYPP450 system. However, certain therapies should be used cautiously with ribavirin due to the potential for enhanced toxicities. Ribavirin in combination with other immunosuppressive therapies, particularly azathioprine or IFN, can lead to severe pancytopenia.[59]

Administration Considerations

Ribavirin administered orally as a solution or capsule has an absolute bioavailability of 40–50% compared with the intravenous or as an aerosol formulation.[59] Oral formulations have enhanced bioavailability when taken with a high-fat meal, and it is recommended to administer both oral formulations with food. Due to the teratogenic potential of ribavirin, it was identified as a hazardous medication on the National Institute for Occupational Safety and Health (NIOSH) list and requires significant safety precautions with its use. The capsules should not be opened, crushed, or broken.[59] Health care providers handling ribavirin must also follow NIOSH recommendations to wear gloves when packaging, administering, or receiving intact capsules. When handling the solution, double gloving, a protective gown, and eye/face protection is required, especially for administration of the oral liquid through a feeding tube.

Nitazoxanide

Therapeutic Uses

Nitazoxanide is a 2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide with an approved Food and Drug Administration (FDA) indication for its antiprotozoal activity to treat diarrhea caused by *Giardia parvum* and *Giardia lamblia*.[68] Nitazoxanide has since been found to have activity against *Cryptosporidium* and in vitro activity against anaerobic gram-positive and gram-negative bacteria.[69, 70] Another studied use of nitazoxanide was for the treatment of influenza.[71] When nitazoxanide was studied for severe acute respiratory illness, no benefit was seen in clinical outcomes, specifically length of hospital stays.[72]

Mechanism of Action

Nitazoxanide interferes with pyruvate ferredoxin oxidoreductase enzyme-dependent electron transfer, thus impairing anaerobic energy metabolism of protozoa.[68] Nitazoxanide is metabolized to its active circulating metabolite tizoxanide.[73] Tizoxanide selectively blocks the posttranslational influenza viral hemagglutinin maturation and intracellular movement in addition to blocking protein implantation into the plasma membrane.[74] Nitazoxanide may potentiate the production of type 1 IFNs produced by host cell fibroblasts that may potentiate antiviral activity via hemagglutinin inhibition.[75]

Rationale for Proposed Therapy

Nitazoxanide has demonstrated in vitro activity against MERS-CoV.[71] An anti-coronavirus effect was observed with nitazoxanide in an in vitro screen of small molecules against a recombinant murine coronavirus.[76] In vitro studies of canine coronavirus found that the use of nitazoxanide inhibited viral replication.[71] Based on this in vitro animal data, it is thought that nitazoxanide may have activity against SARS-CoV-2. Human data are limited regarding the efficacy of nitazoxanide against human coronavirus. In a 260-patient double-blind placebo-controlled trial in patients with influenza-like illness, five participants who received nitazoxanide were coronavirus positive.[72] Subgroup analysis of these five coronavirus-positive patients found no difference in the primary outcome of days of hospitalization (p=0.61).

Dosing and Pharmacokinetics

The recommended nitazoxanide dosing for *Cryptosporidium parvum* or *G. lamblia* is 500 mg oral suspension or tablet every 12 hours for 3 days.[68] The dosing used for acute respiratory illness was twice/day for 5 days, and dose strength was based on age. Patients 12 years of age and older received two 300-mg tablets, children 4–11 years old received 200 mg of the suspension, and toddlers 1–3 years old received 100 mg of the suspension.[72]

It is recommended that nitazoxanide be administered with food because pharmacokinetic studies found increased area under the curve (AUC) and maximum concentration (C_{max}) of tizoxanide.[68] Specifically, a doubling of AUC and 50% increase of C_{max} was observed when the tablet was administered with food. When the suspension was administered with food, there was a 45–50% increase in AUC and up to a 10% increase in C_{max}. An important consideration is that the oral suspension is not bioequivalent to the tablet. The suspension has a bioavailability of 70%, necessitating dose adjustments when transitioning between these dosage forms.[68] In plasma, tizoxanide is more than 99% bound to proteins. Metabolism of nitazoxanide to tizoxanide occurs via hydrolysis and then conjugation via glucuronidation. Nitazoxanide has not been studied in patients with impaired renal and hepatic function, and no dosage adjustment recommendations exist.[68] Data in geriatric and pediatric populations are not available.

Adverse Effects

The most common adverse effects of nitazoxanide are gastrointestinal, mainly abdominal pain, nausea, and headache. Patients may also experience discoloration of eyes and urine, diarrhea, dizziness, gastroesophageal reflux disease, skin rash, or urticaria. Compared with patients receiving standard of care and placebo, patients receiving nitazoxanide did not have additional adverse effects, and both groups of patients experienced gastrointestinal and respiratory effects.[72] Headache and diarrhea were reported most in patients receiving placebo versus low-dose nitazoxanide versus high-dose nitazoxanide for treatment of viral respiratory infection with no significant difference among all three groups.[77]

Administration Considerations

Nitazoxanide is available in dosage forms administered enterally including a controlled-

release film-coated tablet and oral suspension. Nitazoxanide tablets can be crushed and mixed with food. There are no existing data regarding the absorption of nitazoxanide when administered via gastric feeding tubes. However, if gastric feeding tube administration is needed, the oral suspension can be used.

Drug-drug interactions with nitazoxanide are not attributed to cytochrome CYP enzymes because in vitro metabolism data found no significant effect of tizoxanide on these enzyme pathways.[68] Most notably, nitazoxanide may have binding site competition with other highly protein-bound drugs. A narrow therapeutic index drug that would be of concern in this case is warfarin. However, a pharmacokinetic study in which patients received nitazoxanide twice/day for 6 days with a onetime warfarin 25 mg dose compared with patients receiving warfarin did not result in pharmacokinetic or dynamic changes and was well tolerated.[78]

Nelfinavir

Therapeutic Uses

Nelfinavir is a HIV-1 protease inhibitor originally developed for use in combination with antivirals that target HIV via alternative mechanisms. With development of newer combination antivirals for HIV, nelfinavir has fallen out of favor for this indication.[79]

Mechanism of Action

Nelfinavir binds to the site of HIV-1 protease activity and inhibits cleavage of viral Gag-Pol polyprotein precursors into functional proteins that are needed for HIV. What remains are nonviable HIV particles that are no longer infectious.

Rationale for Proposed Therapy

During the 2002 SARS outbreak, nelfinavir was identified as a potential agent with activity against SARS-CoV based on in vitro studies.[80] Nelfinavir was found to inhibit the replication of SARS-CoV in Vero E6 cells originating from the African green monkey. Most recently, nelfinavir was identified via homology models based on three-dimensional SARS structures specifically at the main protease or chymotrypsin-like protease.[81] These models assessed the ability of small molecule drugs to dock to the SARS structures. The SARS-CoV was used because its sequence is 96% similar to that of SARS-CoV-2. Of 30 drugs assessed, nelfinavir was found to have the most promising activity against SARS-CoV-2.

Dosing and Pharmacokinetics

Nelfinavir has not been studied in humans for its efficacy against SARS-CoV or SARS-CoV-2. The recommended dosing of nelfinavir for the treatment of HIV is 750 mg by mouth 3 times/day or 1250 mg by mouth twice/day. The half-life of nelfinavir is 3.5–5 hours. The effective dose for treatment of COVID-19 is unknown. Nelfinavir dosage adjustments do not need to be made with renal impairment because less than 2% of nelfinavir is excreted in the urine.[82] For patients with hepatic impairment, nelfinavir is not recommended in patients with Child-Pugh class B or C.[79, 83, 84] Pharmacokinetics in patients using nelfinavir with chronic liver disease may be unpredictable.[85] No dosage adjustments are recommended for use in patients with Child-Pugh class A impairment.

Nelfinavir is metabolized by CYP3A4 and CYP2C19 and could potentially interact with medications that are inhibitors or inducers of these enzymes. In vitro data found that only CYP3A enzymes were inhibited by nelfinavir at therapeutic concentrations.[82]

Adverse Effects

The major adverse effect of nelfinavir is gastrointestinal intolerance, primarily diarrhea, nausea, and flatulence. A nonspecific rash may also occur. The incidence of other side effects are minimal, occurring less than 2% of the time in phase 2 and 3 trials.[82]

Administration Considerations

Nelfinavir is available in a tablet dosage form. The 250-mg tablets can be dissolved in water and readily dissolve. For patients with a gastric tube as enteral access, nelfinavir can be crushed, dissolved in water, and administered via gastric tube. After dissolving, nelfinavir should be taken or administered immediately. Notably, nelfinavir may have a bitter taste if mixed with acidic food or juice.[82]

Absorption of nelfinavir was found to result in less pharmacokinetic variability and higher nelfinavir levels when taken with food. Nelfinavir has a volume of distribution of 2–7 L/kg and is highly protein bound (more than 98%).[82]

Immunomodulating Therapeutics

Interferon-α

Therapeutic Uses

Interferons are endogenous signaling proteins released by host cells during response to infections or inflammation. Upregulation of IFNs stimulates the immune system to blunt viral replication and eradicate offending pathogens.[86] Two IFNs mediate host immune responses: α and β. Interferon-α elicits a potent host-mediated immune cell response that has generated interest in the treatment of viral diseases such as hepatitis B and C and various cancers such as melanoma and chronic lymphocytic leukemia. Interferon-β has been primarily used in the treatment of the autoimmune condition multiple sclerosis.[87] These nonspecific immunomodulatory effects have gained attraction by investigators for other viral illnesses including COVID-19.

Mechanism of Action

During the 2002 SARS outbreak, it was observed that after viral inoculation, SARS-CoV was able to effectively evade upregulation of IFNs in human macrophages. This allowed for continued viral replication due to suppression of the innate immune response.[87] Two IFN products are available, α and β. It is currently unknown whether both products would influence coronavirus disease expression. Interferon-α has the most studies related to its use.

Rationale for Proposed Therapy

Thus far, human data for the use of IFN-α for novel coronaviruses are sparse. During the SARS outbreak, pegylated IFN-α was assessed in an in vitro analysis of macaque cells at different periods of SARs exposure.[88] When used before SARS inoculation, IFN-α reduced viral replication and excretion. However, these results were not observed post-SARS exposure.[88] An in vitro analysis assessing IFN-α as monotherapy for MERS demonstrated the serum concentrations required to effectively inhibit viral replication were higher than what can be safely achieved in humans.[63] Nevertheless, in vitro isolates of IFN-α or -β as a multimodal regimen with ribavirin for SARS displayed potent synergy against the virus.[89, 90] In vivo studies have yet to be able to replica the same benefits, with some studies showing no influence on the disease course for MERS, whereas others suggest a small improvement in survival at 14 days but not 28 days when used in combination with ribavirin.[91, 92] These viruses may display different in vitro and in vivo susceptibilities than the current SARS-CoV-2; extrapolation to the current COVID-19 pandemic is difficult. This has not dampened the potential application of this therapy, and investigators await the results of ongoing studies assessing the efficacy of IFN-α-2b as a part of combination therapy with ribavirin for COVID-19 to further elucidate any benefit from IFN treatment.[93, 94]

Dosing and Pharmacokinetics

Interferon-α-2b also comes as a pegylated form to prolong its half-life from 4.6 hours to 22–60 hours, permitting a lower dosing frequency.[87] Due to the lack of established human data with IFNs for COVID-19, this therapy should only be considered for COVID-19 as a part of a clinical trial. There is no established dosing regimen for IFN in the treatment of COVID-19. The only in vivo data are with IFN-α-2a for the treatment of MERS using a dose of 180 μg per week for 2 weeks, similar to hepatitis B virus.[92] There is no established dosing regimen for IFN in the treatment of COVID-19. The only study currently recruiting at the time of this publication is using IFN-β-1b at a dose of 0.25 mg (8 million IU) on day 1, 3, and 5 in combination with other therapies (ribavirin, LPV/r).[93] Additional studies evaluating IFN-α-1b are evaluating its utility as an inhaled therapy.[94]

If used as a part of a trial, there are key clinical considerations to consider for safe use. The drug labeling provides a cautionary statement for use in Child-Pugh class B or C.[87] Renal elimination accounts for 30% of total clearance dose reductions required for patients with a Cl_{cr} below 50 ml/minute when IFN-α is used in combination with ribavirin for hepatitis C.[87] Given that these agents are both under investigation for COVID-19, if used as a part of combination therapy, the same precaution should be considered. Interferon therapies have an increased risk of adverse effects when used during renal replacement therapy; thus caution is recommended in this population.[95, 96]

Interferon does not pose a risk of drug-drug interactions through CYP enzyme pathways. Concomitant medications that enhance the myelosuppressive or hepatotoxic effects of IFN should be used sparingly.[87]

Adverse Effects

Interferons are associated with significant adverse reactions, even when used as a short-term therapy. Injection site reactions resulting in flulike symptoms (fever, myalgias, and headaches) occur within the first 2–8 hours after administration. Rotation of injection sites, application of ice before and after application, and premedication with acetaminophen can mitigate these reactions. Additional adverse reactions include leukopenia, lymphopenia, autoimmune hepatitis, and thyroid disease. Patients exposed to IFNs for currently approved indications can develop neutralizing antibodies that reduce the therapeutic efficacy of this agent. The development of neuropsychiatric adverse effects is not expected to occur with short-term use.[97] The safety of IFN in pregnancy has not been established.[87]

Administration Considerations

Interferon is available in injectable and inhaled formulations. The current study is enrolling patients using β-1b injected subcutaneously in the abdomen or thigh.[93]

Baricitinib

Therapeutic Uses

Baricitinib is a Janus kinase (JAK) inhibitor originally developed for the treatment of rheumatoid arthritis. It is approved by the FDA for moderate or severe active rheumatoid arthritis in patients who have not responded to one or more tumor necrosis factor antagonists.

Mechanism of Action

Baricitinib reversibly and selectively inhibits JAK1 and JAK2 with less inhibition of JAK3 and tyrosine kinase. Inhibition of JAK results in inability of signal transmission from cytokine or growth receptors resulting in decreased hematopoiesis and immune cell function.[98] This inhibition of signal transmission prevents phosphorylation and thus activation of signal transducers and activators of transcription. Baricitinib has a high affinity for associated protein kinase 1 (AAK1) binding and could prevent the intracellular passage of viral cells and development of viral particles.[99]

Rationale for Proposed Therapy

COVID-19 may result in secondary hemophagocytic lymphohistiocytosis (sHLH) as a result of viral infection.[100] Patients with COVID-19 have exhibited ferritin and inflammatory marker elevations similar to sHLH including elevated interleukin (IL)-2, IL-7, granulocyte stimulating factor, and tumor necrosis factor (TNF)-α. Evaluation of risk factors for mortality of COVID-19 cases in Wuhan found ferritin and IL-6 levels to be higher in those who ultimately died versus survivors (p<0.001).[101] Considering the potential for increased lung injury with corticosteroid use in patients with COVID-19 and reported use of tocilizumab for COVID-19, JAK-STAT inhibitors were theorized to have an effect on the hyperinflammatory state that occurs in COVID-19. Baricitinib may also prevent endocytosis and viral infection by inhibiting AAK1 activity. Baricitinib has not been studied in humans for COVID-19.

Dosing and Pharmacokinetics

Baricitinib is typically dosed as 2 mg/day by mouth for rheumatoid arthritis.[98] No data exist for treatment of COVID-19; however, it is proposed that a 7- to 14-day course would be needed.[102] Dose adjustments are recommended for patients with lymphopenia, neutropenia, and anemia.[98] It is recommended to hold baricitinib in patients with an absolute lymphocyte count less than 500 cells/mm^2, an absolute neutrophil count less than 1000 cells/mm^2, and hemoglobin less than 8 g/dl. In patients with hepatic impairment, baricitinib is not recommended. Dose adjustments are recommended with renal impairment. For patients with an estimated glomerular filtration rate (eGFR) less than 30 ml/minute/1.73 m^2, it is recommended to hold baricitinib. For patients with an eGFR 30–60 ml/minute/1.73 m^2, it is recommended to decrease dose to 1 mg once/day. There are no dosing recommendations for patients requiring CRRT.

Baricitinib reaches peak concentrations within 1 hour of oral administration with steady state achieved at 2–3 days.[98] Baricitinib has an oral bioavailability of 80% and is not significantly impacted by taking with or without food. The baricitinib volume of distribution is 76 L; it is 50% bound to plasma proteins and 45% bound to serum proteins. It is a substrate of P-gp, breast cancer resistance protein OAT, and multidrug and toxin extrusion protein transporters.

Metabolism of baricitinib occurs mainly by CYP3A4, and elimination is ~75% renal.

Relevant drug-drug interactions with baricitinib include strong OAT 3 inhibitors that may increase baricitinib exposure.[98] For patients concomitantly taking strong OAT 3 inhibitors, the recommended dose of baricitinib is 1 mg once/day.

Adverse Effects

Several boxed warnings exist for baricitinib including risk of infection, particularly upper respiratory tract infection, malignancy, and thrombosis.[98] Of note, these side effects were higher in patients receiving the 4-mg dose of baricitinib that is not a recommended dose due to these safety concerns. Patients in clinical trials also experienced increased incidence of neutropenia, platelet elevations, aminotransferase elevations, lipid elevations, creatinine elevations, creatine phosphokinase elevations, and nausea. Monitoring for long-term treatment of rheumatoid arthritis is recommended with baseline complete blood counts including neutrophils, liver function tests, and lipids.[98] Monitoring for signs and symptoms of infection while treating with baricitinib is recommended in addition to skin examinations in patients at an increased risk for skin cancer.

Administration Considerations

Baricitinib is available as a film-coated immediate-release tablet for enteral administration.[98] It can be given with or without consideration of food. No data are available regarding crushing baricitinib and administration via gastric feeding tubes. Although baricitinib is not on the NIOSH list of medications, it is carcinogenic by virtue of the adverse effect profile, and it may be treated as a hazardous drug.

Tocilizumab

Therapeutic Uses

Tocilizumab is a monoclonal antibody with FDA approval for chimeric antigen receptor (CAR)-T cell-induced cytokine release syndrome (CRS), giant cell arteritis, rheumatoid arthritis, and polyarticular or systemic juvenile idiopathic arthritis.[103]

Mechanism of Action

Evolving data suggest patients with severe COVID-19 experience significant lung injury secondary to a surge of inflammatory cytokines, resulting in a cytokine storm. Viral replication activates the innate immune system to secrete various signaling proteins such as ILs that results in hyperinflammation and further lung damage. Interleukin-6 is a key inflammatory protein involved in this pathway.[100] Tocilizumab binds to IL-6 receptors, thereby blunting cell signaling and effectively downregulating the excess inflammatory response.[103]

Rationale for Proposed Therapy

The rationale for use of tocilizumab in COVID-19 stems from data discovered with SARS and MERS. The SARS patients were noted to have CRS as a result of proinflammatory marker release including IL-6 and TNF-α.[104] Patients with MERS were discovered to have elevations of IL-6, IL-8, and IL-1β.[105] The data from Wuhan in critically ill patients with COVID-19 have also found increased levels of cytokines including IL-6 and granulocyte-colony stimulating factor.[8, 106]Lung tissue obtained postmortem from a patient with COVID-19 showed elevated inflammatory factors suggestive of a cytokine storm.[107] Interleukin-6 may be a key driver of the robust inflammatory response within the lungs of ICU patients with COVID-19. Recently published data from Wuhan indicate that tocilizumab added to lopinavir, methylprednisolone, and oxygen therapy in 20 patients with severe COVID-19 resulted in rapid reductions in fever in all patients, improvement in oxygenation for 75%, and facilitated discharged from the hospital in 95% of patients.[108] Additional studies are underway with tocilizumab combined with other antivirals or compared against renal replacement therapy for management of CRS associated with COVID-19.[109, 110] Sarilumab, another anti-IL-6 antibody, is currently under evaluation for the treatment of COVID-19. It will be studied against supportive care measures and provide enhanced insight into the utility of targeting this pathway.[111]

Dosing and Pharmacokinetics

Tocilizumab for most indications is weight based with a maximum dose of 800 mg. The dosing of tocilizumab for COVID-19 is not well established. When used in a case series of patients with COVID-19, a onetime dose of intravenous tocilizumab 400 mg was administered.[108, 112] For CRS secondary to chimeric

antigen receptor CAR T-cell therapy, three additional doses of tocilizumab can be given with at least 8 hours between each dose. In the COVID-19 reports, three patients received an additional dose of tocilizumab 12 hours later as a result of continued fevers.[108]

Tocilizumab AUC varies based on body weight, and the Vd of intravenous tocilizumab at steady state is 6.4 L.[103] There are no published data regarding the use of tocilizumab 400 mg in obese patients with COVID-19 and whether the 400-mg dose is adequate. The half-life of tocilizumab is concentration dependent, at 11 days when dosed 4 mg/kg and 13 days when dosed 8 mg/kg. Tocilizumab should be held when the absolute neutrophil count is 1000 cells/mm^2 or below, platelet count is 100,000 cells/mm^2 or below, or liver enzymes are more than 3–5 times the upper limit of normal. This is particularly relevant for the treatment of COVID-19 that was demonstrated to elevate liver enzymes in severe cases.[113] Tocilizumab elimination is not influenced by renal dysfunction. No dose adjustments are required. In patients receiving tocilizumab for COVID-19, only one patient had a history of chronic kidney disease, and no patients had reported hepatic impairment.[108]

Adverse Effects

Limited efficacy data with tocilizumab should be weighed against its significant cost and potential for toxicities. Secondary to interference with the host immune response, infections ranging from bacterial, viral, and fungal sources may develop.[103] Patients should be screened for active or latent tuberculosis infection before administering tocilizumab. Gastrointestinal perforation after the use of tocilizumab was reported in patients with a history of diverticulitis or receiving high-dose corticosteroids.[103] Infusion reactions causing hypertension, headache, and skin reactions within 24 hours of administration were reported after administration of tocilizumab.[103]

Administration Considerations

Tocilizumab is recommended to be administered intravenously over 1 hour.[112, 103] Tocilizumab should not be administered in the same line with other medications because it has not been studied for compatibility.[103]

Pertinent drug-drug interactions with tocilizumab may occur as a result of increased CYP450 enzyme activity. In vitro studies reported that tocilizumab may increase CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 activity. In vivo studies reported that tocilizumab may interact with simvastatin via increased activity of CYP3A4, resulting in decreased simvastatin exposure. Findings were also similar when omeprazole and tocilizumab were combined, resulting in decreased omeprazole AUC through increased CYP19 activity.

Convalescent Plasma Therapy

Passive immunity delivered as anti-coronavirus antibodies from convalescent human plasma may offer a novel therapeutic approach for COVID-19. The proposed mechanism of benefit from convalescent human plasma derived from survivors of the coronavirus is the transfer of passive immunity in an effort to restore the immune system during critical illness and neutralize the virus to suppress viremia.[114] The main driver for the investigation of convalescent human blood products in the treatment of COVID-19 originated from its use in the H1N1 pandemic, during which patients derived a clinically significant mortality benefit and improved viral clearance from convalescent blood products.[115]

In a retrospective review of 40 patients with SARS who failed treatment with methylprednisolone and ribavirin at 3 days, 74% (19) of patients who received convalescent plasma were discharged by day 22 compared with only 19% (21) of patients who received high-dose corticosteroids (p<0.001). Five deaths were reported in the steroid group compared with no deaths with convalescent plasma. To obtain the greatest benefit from convalescent plasma, treatment should be used early in the course of disease (before day 16) because viremia from SARS was shown to peak in the first week of treatment followed by a primary immune response by days 10 to 14.[116] Preliminary data from ongoing convalescent plasma therapy data in the COVID-19 outbreak suggest improvement in clinical symptoms with no signal of adverse effects.[117]

Targeted anti-SARS-CoV-2 antibodies that allow for a more selective therapy against coronavirus are in development, and some companies have begun active recruitment for investigation into its clinical efficacy and safety treatment of COVID-19.[118] Takeda Pharmaceutical has announced investigation into a new plasma-derived therapy coined TAK-888. This plasma-

derived therapy involves removing plasma from COVID-19 survivors, extracting coronavirus-specific antibodies to administer to infected patients to stimulate a potent immune response against SARS-CoV-2. Convalescent therapy remains in the experimental phase, but appears it may favorably influence the treatment course, and enrollment of patients into a clinical trial will aid in defining its role in therapy.

Corticosteroids

Given lack of efficacy and risk of delayed viral clearance, the World Health Organization consensus document on the management of COVID-19 strongly recommends against the use of corticosteroids unless alternative indications are present. Acute lung injury and respiratory distress syndrome secondary to systemic inflammation are well-characterized sequelae of SARS and MERS outbreaks with pulmonary histology demonstrating evidence of inflammation and diffuse alveolar damage.[119] Corticosteroids were proposed to be of benefit in suppression of lung inflammation in MERS and SARS due to their immunomodulatory properties. However, clinical data are now clear that patients derive no benefit from corticosteroids in the management of SARS, MERS, or COVID-19 but have instead demonstrated evidence of increased risk of harm including prolonged mechanical ventilation, avascular necrosis, delayed viral clearance, and secondary infections.[120, 121]

A retrospective observational study of critically ill patients with MERS who received hydrocortisone 300 mg per day did not find a 90-day mortality benefit (adjusted odds ratio 0.8, 95% confidence interval [CI] 0.5–1.1, p<0.12) but did find delayed viral clearance (adjusted HR 0.4, 95% CI 0.2–0.7, p<0.0005).[122] The lack of survival benefit was further supported by a systematic review of corticosteroids in patients with SARS but showed an increased risk of psychosis, avascular necrosis, prolonged viremia, and hyperglycemia with corticosteroid treatment.[120] Although severe, potentially life-threatening ARDS can occur, generalizing the evidence for corticosteroids to the COVID-19–associated ARDS is problematic and fails to account for the differing pathogenesis of viral-induced lung injury.[121]

Corticosteroids should only be considered if required for an alternative indication (i.e., septic shock, bronchoconstriction). Despite the lack of benefit defined in previous trials, a clinical trial is actively recruiting to assess the efficacy and safety of methylprednisolone 1 mg/kg/day for a duration of 7 days in noncritically ill patients to further identify the risks and benefits of therapy.[123]

Other Emerging Therapies for Treatment of COVID-19

In addition to the drug therapies previously discussed, several additional drugs are being evaluated as potential therapies for COVID-19 in clinical trials. Arbidol, a drug used in Russia and China for prophylaxis and treatment of influenza and respiratory viral infections, works by blocking viral fusion to the target cell membrane and has demonstrated activity against several viruses including SARS.[124] Arbidol is currently being evaluated for the treatment of COVID-19 in several studies in China and is currently a recommended treatment option for COVID-19 there. Arbidol is not available in the United States. Favipiravir, a drug licensed in Japan for the treatment of influenza, is another potential agent due to its activity against a wide spectrum of RNA viruses including coronaviruses.[125] Several studies are underway evaluating favipiravir for the treatment of COVID-19. Other antiviral agents being evaluated in China for the treatment of COVID-19 include antiretroviral agents darunavir/cobicistat and emtricitabine/tenofovir alafenamide, as well as the influenza drug baloxavir. Finally, oseltamivir, a neuraminidase inhibitor used for treatment of influenza, is also being studied for treatment of COVID-19. However, oseltamivir is unlikely to be active against SARS-CoV-2 based on previous studies with SARS-CoV.[61]

Drugs to decrease the inflammation associated with COVID-19 are also being evaluated. One of these drugs is thalidomide that may decrease inflammation through its antiinflammatory and immunomodulatory effects.[126]

Conclusions

The COVID-19 pandemic has presented an enormous global health crisis. The pharmaceutical industry is working to develop novel treatments targeted at SARS-CoV-2. In the meantime, the medical community is trialing a variety of therapies that target different antiviral and immunomodulating mechanisms to combat this virus. Some of the drugs are investigational, and some are old drugs being repurposed for a new pathogen. As we gain more information both about the effectiveness of the drugs against

SARS-CoV-2 and their pharmacokinetics, especially in the complex setting of critical illness, we will be better equipped to optimize therapeutic strategies.

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