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Health Care Campus

Pharmacologic Treatments for COVID-19 Review

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Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)
James M. Sanders **et al. JAMA,** April 13, 2020

This review offers a good summary of current evidence and ongoing RCTs regarding COVID-19 pharmacological treatment: both drugs which target the virus and drugs that modulate the immune system and the cytokine storm.

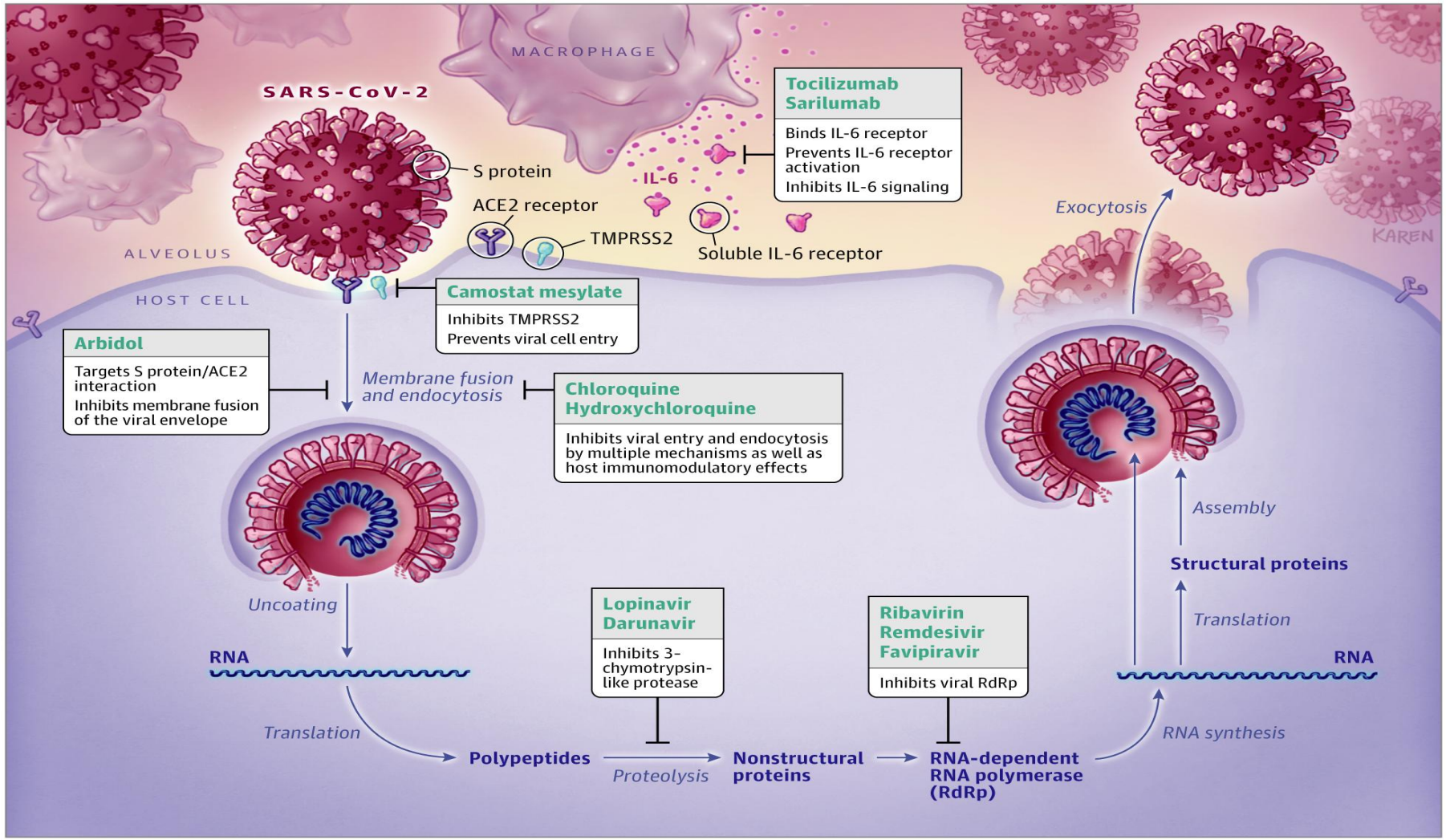

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Table 1. Summary of Pharmacology for Select Proposed COVID-19 Treatments

Agent	Target	Adult dose/administration	Contraindications	Toxicities	Major drug-drug interactions	Special populations
Repurposed agents						
Chloroquine phosphate (Aralen/generic)[9-14]	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells	500 mg by mouth every 12-24 h × 5-10 d. Available as: 250-mg tablets (salt); 500-mg tablets (salt); 500-mg tablets of chloroquine phosphate (salt) = 300-mg chloroquine base. Dose adjustments: Kidney: creatinine clearance <10 mL/min administer 50% of dose. Hepatic: No dose adjustments in hepatic impairment recommended; use with caution. Administration: Preferable to avoid crushing. If needed, may be crushed and mixed with jam, pasteurized yogurt or similar foods	Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of formulation. Presence of retinal or visual field changes of any etiology (unless benefit outweighs risk)	Common: Abdominal cramps, anorexia, diarrhea, nausea, vomiting. Major: Cardiovascular effects (including QTc prolongation), hematologic effects (including hemolysis with G6PD deficiency, use if benefit outweighs risks), hypoglycemia, retinal toxicity, neuropsychiatric and central nervous system effects, idiosyncratic adverse drug reactions	CYP2D6 and CYP3A4 substrate	May be used in pregnancy if benefit outweighs risks
Hydroxychloroquine sulfate (Plaquenil/ generic)[9-11,15-20]	Hydroxychloroquine shares the same mechanism of action as chloroquine	400 mg by mouth every 12 h × 1 d, then 200 mg by mouth every 12 h × 4 d; alternative dosing: 400 mg by mouth daily × 5 d or 200 mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water OR compounded into an oral solution	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative, or any component of the formulation	Adverse drug reactions similar to chloroquine but less common	CYP2D6, CYP3A4, CYP3A5, and CYP2C8 substrate	May be used in pregnancy if benefit outweighs risks
Lopinavir/ritonavir (Kaletra)[21-26]	3CL protease	400 mg/100 mg by mouth every 12 h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-mg/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution, take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes	Hypersensitivity to lopinavir/ritonavir or any of its ingredients, including ritonavir. Co-administration with drugs highly dependent on CYP4503A. Co-administration with potent CYP450 3A inducers	Common: gastrointestinal intolerance, nausea, vomiting, diarrhea. Major: Pancreatitis, hepatotoxicity, cardiac conduction abnormalities	CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer. P-gp substrate; UGT1A1 inducer	May be used in pregnancy; avoid oral solution if possible due to ethanol content
Umifenovir (Arbidol)[27-29]	S protein/ACE2, membrane fusion inhibitor	200 mg every 8 h by mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Dose adjustments: Kidney: no dose adjustment necessary. Hepatic: No specific recommendations available, caution in those with hepatic impairment. Administration: Bioavailability 40%	Known hypersensitivity to umifenovir	Allergic reaction, gastrointestinal upset, elevated transaminases	Metabolized by CYP3A4, monitor with strong inducers/inhibitors	Contraindicated in children <2 y of age (increased sensitivity)

Investigational agents						
Remdesivir[30-32]	RNA polymerase inhibitor	200 mg × 1, 100 mg every 24 h IV infusion. Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR <30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion	Exclusion criteria based on specific protocols	Elevated transaminases (reversible), kidney injury	Not a significant inducer/inhibitor of CYP enzymes, monitor with strong inducers/inhibitors	Safety in pregnancy unknown, currently recommended to avoid
Favipiravir[33,34]	RNA polymerase inhibitor	Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available, Hepatic: Dose adjustment considered in Child-Pugh C, increased exposures observed in Child-Pugh class A to C. Administration: Tablet can be crushed or mixed with liquid, bioavailability >95%	Exclusion criteria based on specific protocols	Hyperuricemia, diarrhea, elevated transaminases, reduction in neutrophil count	CYP2C8 and aldehyde oxidase inhibitor, metabolized by aldehyde oxidase and xanthine oxidase	Contraindicated during pregnancy, metabolite found in breast milk
Adjunctive therapies						
Tocilizumab (Actemra)[35,36]	IL-6 inhibition- reduction in cytokine storm	400 mg IV or 8 mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response. Available as: IV infusion injection: 80 mg/4 mL (20 mg/mL); 200 mg/10 mL (20 mg/mL); 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion. Dose adjustments: Kidney: No dose adjustments recommended in mild or moderate kidney impairment. Not studied in patients with severe impairment. Hepatic: No dose adjustments recommended (not studied); initiate based on benefit. Administration: Infuse over 60 min, should not be infused concomitantly in the same IV line with other drugs	Known hypersensitivity to tocilizumab or any components of the formulation. Caution in patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50 000/μL)	Common: Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion related reactions. Major: Hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity reactions	In vitro data suggested that IL-6 reduces mRNA expression for several CYP450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. May decrease levels of substrates	Safety in pregnancy unknown; may cause harm to the fetus

Abbreviations: ACE2, angiotensin-converting enzyme 2; AST, aspartate aminotransferase; 3CL, 3-chymotrypsin-like; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; G6PD, glucose-6-phosphate-dehydrogenase; GFR, glomerular filtration rate; IV, intravenous; P-gp, P-glycoprotein; UGT1A1, UDP glucuronosyltransferase family 1 member A1.

Corticosteroids: the potential harms and lack of proven benefit for corticosteroids cautions against their routine use in patients with COVID-19 outside an RCT unless a concomitant compelling indication, such as chronic obstructive pulmonary disease exacerbation or refractory shock exists.

Clinical Treatment Guidance and Other Useful Resources

International and Select National or Institutional Clinical Management Guidance

- World Health Organization Clinical Management Guidance (interim guidance, updated March 13, 2020)
  - https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-susp
- US Centers for Disease Control and Prevention COVID-19 clinical care (interim guidance, updated March 7, 2020)
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
- Chinese National Health Commission novel coronavirus pneumonia diagnosis and treatment plan (provisional 7th edition, updated March 3, 2020)
  - English translation: https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf
- Italian Society of Infectious and Tropical Diseases handbook for care of people with COVID-19 (edition 2.0, updated March 13, 2020)
  - English translation: https://drive.google.com/file/d/1eXE6espkYp6_k2XCyTf_6kgT6tFbnQjg/view
- University of Washington
  - https://covid-19.uwmedicine.org/Pages/default.aspx
- JAMA Network COVID-19 site
  - https://jamanetwork.com/journals/jama/pages/coronavirus-alert

Clinical Trials Registries/Resources

- Clinical trials (US)
  - https://clinicaltrials.gov/ct2/search
- Clinical trials (China)
  - http://www.chictr.org.cn/searchprojen.aspx
- National Institutes of Health COVID-19 page
  - https://www.nih.gov/health-information/coronavirus

Guidance for Special Populations

- Solid organ transplantation
  - https://www.myast.org/covid-19-information#
- Surviving Sepsis Campaign: guideline on the management of critically ill adults with COVID-19
  - https://jamanetwork.com/journals/jama/fullarticle/2763879
- Care of patients with cancer during COVID-19 pandemic
  - https://jnccn.org/fileasset/jnccn1804-Ueda_20118_preprint.pdf
- Pregnancy
  - https://www.acog.org/topics/covid-19
- Persons with HIV
  - https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv--interim-guidance-/0