Treatment Armamentarium of COVID-19: Evolving Strategies and Evidence So Far

Swapnil Dhampalwar , Sanjiv Saigal , Arvinder S. Soin

Institute of Liver Transplantation & Regenerative Medicine, Medanta- The Medicity, Gurugram, India

The outbreak of SARS-CoV-2 started in Hubei province of China in December 2019 and rapidly spread all over the world. It has infected more than 7 million people worldwide and has pushed half of the world in a state of lockdown. There is an urgent unmet need of interventions both for prevention and treatment of this disease and more than 500 clinical trials are ongoing in this regard. At present, no study with robust methodology have clearly demonstrated benefits of hydroxychloroquine for treatment, preexposure prophylaxis in healthcare workers or post exposure prophylaxis in COrona VIrus Disease-2019. Remdesivir has been shown to have modest benefits in moderate to severe disease, if administered early. Given the rapid pace of clinical information and discoveries, it is important for clinicians to be up to date with the latest, evidence-based treatment options available for this novel disease. Keeping up with this current pace of information, we review the clinical studies of different therapeutic options available to treat SARS-CoV-2. (J Clin Exp Hepatol 2020;10:599–609)

In December 2019, China reported cluster of cases of pneumonia of unknown origin in Wuhan, Hubei province, which was communicated to World Health Organization (WHO) China office on December 31, 2019. With worldwide rapid spread of disease, the International Health Regulations Emergency Committee of WHO declared the outbreak as a "public health emergency of international concern" on January 30, 2020.[1] The disease is caused by a new strain of beta corona virus,[2] which was initially called as 2019 novel Corona virus (2019-nCoV) and subsequently designated as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by International Committee on Taxonomy of Viruses.[3] On February 11, 2020, WHO designated the disease as *CO*rona *VI*rus *D*isease-20*19* (COVID-19). The virus continues to have unprecedented spread across the globe with significant impacts on healthcare systems and global economy. The outbreak was declared as pandemic on March 11, 2020, by WHO (Figure 1).

As per Center for Systems Science and Engineering at Johns Hopkins University, SARS-CoV-2 has infected 7,435,727 people worldwide causing 418,203 deaths. India reported its first case on January 30, 2020 with total number cases 286,577 with 8102 deaths as of June 11, 2020, 11.00pm IST.[4] There is no approved therapy for COVID-19 at present, and more than 500 clinical trials are ongoing. The US FDA has authorized the use of hydroxychloroquine (HCQ) on March 20, 2020, and remdesivir on May 1, 2020, on emergency basis for treating patients with COVID-19.[5] Keeping up with the current pace of information, we review the clinical studies of different therapeutic options available to treat COVID-19 as on June 11, 2020.

VIRAL LIFECYCLE AND PATHOGENESIS

New coronaviruses appear to infect humans periodically because of their wide distribution, zoonotic reservoirs, genetic diversity with frameshift genetic recombination and increased human-animal interface activities. SARS-CoV-2 belongs to *Betacoronavirus* genus which includes Bat SARS-like coronavirus, SARS-CoV, and Middle East Respiratory Syndrome (MERS)-CoV. Genome-wise analysis reveals about 96% genetic similarity of SARS-CoV-2 with Bat SARS-like coronavirus, 80% with SARS-CoV, and 50% with MERS-CoV. Bats are the wild reservoirs of Betacoronaviruses. SARS-CoV and SARS-CoV-2 attach to the host cell through angiotensin converting enzyme 2 (ACE-2) receptor while MERS-CoV through dipeptidyl peptidase 4. SARS-CoV-2 has lower case fatality rate (around 3%) and higher transmissibility (basic reproduction number R_0 2-2.5) as compared with SARS-CoV (9.5% and 1.7-1.9, respectively) and MERS-CoV (34.4% and 0.7, respectively).[6]

SARS-CoV-2 is an enveloped, non-segmented, positive sense, single-stranded RNA virus. It has 4 structural proteins including spike (S) glycoprotein, envelope (E) glycoprotein, membrane (M) glycoprotein, nucleocapsid (N) protein, and several other non-structural proteins.

Keywords: coronavirus disease, COVID-19, COVID-19 treatment, novel coronavirus, SARS-CoV-2
Received: 11.5.2020; *Accepted:* 5.7.2020; *Available online 16 July 2020*
Address for correspondence. Sanjiv Saigal, Director – Transplant Hepatology, Medanta Institute of Liver Transplantation and Regenerative Medicine, Medanta The Medicity, Sector 38, Gurgaon, Delhi (NCR), India.
E-mail: sanjivsaigal@hotmail.com
Abbreviations: ARDS: Acute Respiratory Distress Syndrome; COVID-19: *CO*rona *VI*rus *D*isease - 2019; CQ: Chloroquine; HCQ: Hydroxychloroquine; IL-6: Interleukin-6; INF: Interferon; LPV/TRV: Lopinavir/ritonavir; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; TCZ: Tocilizumab; WHO: World Health Organization
https://doi.org/10.1016/j.jceh.2020.07.001

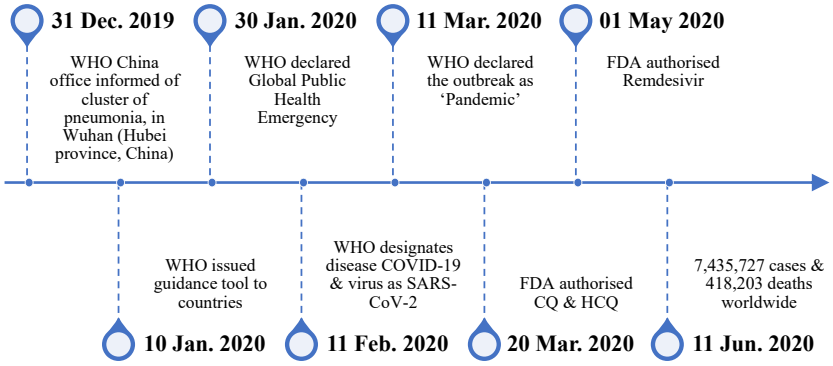

Figure 1 Timeline of events.

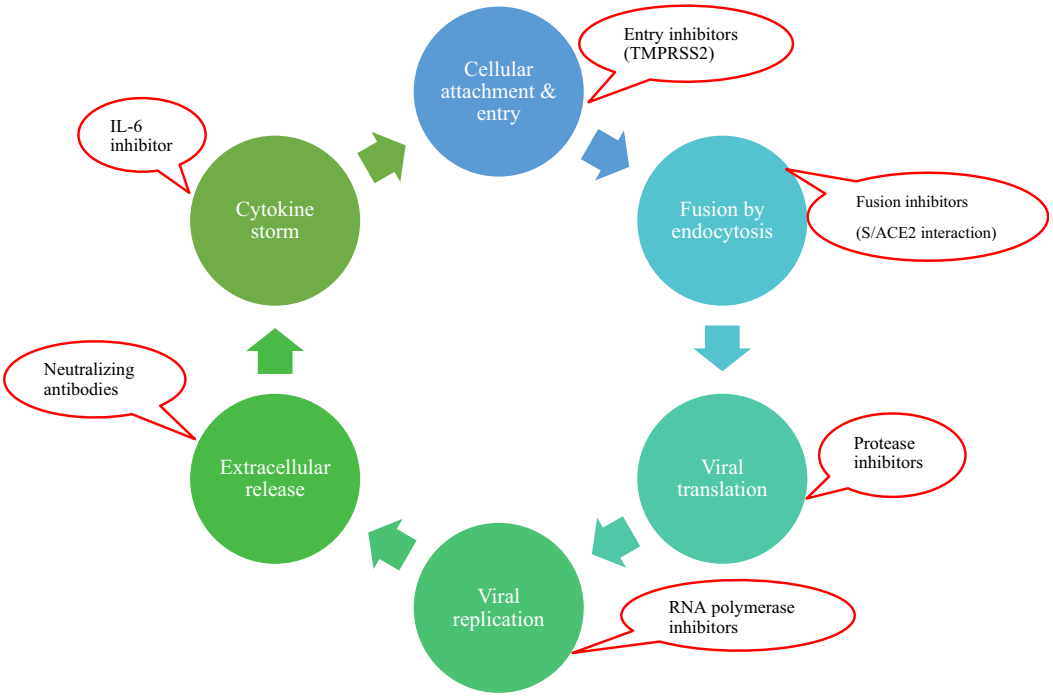

Figure 2 Lifecycle of the virus and potential therapeutic targets. ACE2, angiotensin converting enzyme 2; TMPRSS2, type 2 transmembrane serine protease.

Table 1 Treatment Options for SARS-CoV-2.

Class	Drugs
Entry inhibitors	Camostat mesylate (TMPRSS2)
Fusion inhibitors	Umifenovir (Arbidol)
Endocytosis inhibitors	Chloroquine, Hydroxychloroquine, JAK-STAT inhibitors (Baricitinib, Ruxolitinib, Fedratinib)
Protease inhibitors	Lopinavir-ritonavir, Darunavir
RNA-dependent RNA polymerase inhibitors	Remdisivir, Favipiravir, Ribavirin
Immunomodulators	IL-6 inhibitors (Tocilizumab, Sarilumab), Chloroquine, Hydroxychloroquine
Neutralizing antibodies	Convalescent plasma exchange

Table 2 Clinical Studies of Hydroxychloroquine ± Azithromycin in Patients With COVID-19.

Authors	Type of study (No. of patients)	Treatment arms	Virologic outcomes	Clinical outcomes	ICU stay	Adverse events	Death	Comments
Gao J *et al.* Feb 2020, China[13]	Case series (n > 100)	CQ	Promotes virus negative conversion	Improved lung imaging findings and shortens disease course	NR	NR	NR	No analyzable data reported
Chen J *et al.* Mar 2020, China[15]	RCT (1:1) (n = 30)	HCQ 200 mg 12hrly x 5 days vs Control	Throat swab on D7 (86.7% vs 93.3%), time to nucleic acid conversion (4 vs 2 d)	No difference in time to fever remission, radiological progression (33.3% vs 46.7%)	None	4/15	None	No significant change in viral load, mild disease, small number
Chen Z *et al.* Apr 2020, China[16]	RCT (1:1) (n = 62)	HCQ 200 mg 12hrly x 5 days vs Control	NR	Significant improvement in time to clinical recovery (fever and cough remission), improved pneumonia (80.6% vs 54.8%)	4/31 in control arm	2/31	None	Mild disease with small number of patients
Gautret P *et al.* Mar 2020, France[17]	Prospective, open-label non-RCT (n = 42)	HCQ 200 mg 8hrly (n = 14) for 10 days ± AZT 500 mg on D1, 250 mg D2-5 (n = 6) vs Control	Nasopharyngeal swab negative on D6 (100% in combination vs 57.1% in HCQ alone vs 12.5% in control)	NR	None	NR	None	Unequal arms, 6 lost to follow-up, mild disease
Molina JM *et al.* Mar 2020, France[19]	Prospective observational study (n = 11)	HCQ 200 mg 8hrly for 10 days + AZT 500 mg on D1, 250 mg D2-5 No control arm	Nasopharyngeal swabs positive in 8/10 (80%) patients at D5-6	Oxygen therapy 91%, ICU transfer 18%, Death 9%	2/11	1/11	1/11	Small number of patients with severe disease, clinical outcomes not well defined
Gautret P *et al.* Apr 2020, France[18]	Prospective observational study (n = 80)	HCQ 200 mg 8hrly for 10 days + AZT 500 mg on D1, 250 mg D2-5 No control arm	Nasopharyngeal viral load (83% negative at D7, 93% at D8), Virus cultures negative in 97.5% D5	Oxygen therapy 15%, ICU transfer 3.8%, Death 1.2%, Discharge 81.2%, mean length of stay of 5 days	3/80	7/80	1/80	First study with better case definition, 6 patients from previous study included

(*Continued on next page*)

Table 2 (*Continued*)

Authors	Type of study (No. of patients)	Treatment arms	Virologic outcomes	Clinical outcomes	ICU stay	Adverse events	Death	Comments
Geleris J *et al.* May 2020, USA[20]	Observational study (n = 1376)	HCQ 600 mg 12hrly on D1, 400 mg 12hrly D2-5 (n = 811) vs Control	NR	Respiratory failure developed in 346 patients (25.1%); 180 patients were intubated, and 166 died without intubation	NR	25.1%	NR	No significant association with higher or lower risk of death or intubation; largest observational study with negative results

Abbreviations: AZT, azithromycin; CQ, chloroquine; COVID-19, COrona VIrus Disease-2019; HCQ, hydroxychloroquine; ICU, intensive care unit; NR, not reported; RCT, randomized control trial.
Modified from Taccone FS, Gorham J, Vincent JL. Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. Lancet Respir Med 2020.[10]

COVID-19

It is essential to understand the lifecycle of the virus and pathogenesis as it offers insights into potential therapeutic targets. The process of cellular entry of virus starts by attachment of S protein with angiotensin converting enzyme 2 (ACE-2) receptor on host cells (i.e. pneumocytes). Attachment occurs *via* binding domain of S protein to ACE-2 which is followed by fusion of viral membrane to host cell. After fusion, type 2 transmembrane serine protease (TMPRSS2) present on host cells clears ACE-2 and activates S protein. Activation of S protein causes conformational change allowing cellular entry of the virus. Thus, both ACE-2 and TMPRSS2 are important determinants of cellular entry and fusion (Figure 2).[7]

After cellular entry, genetic material of the virus (i.e. mRNA) gets injected into the cytoplasm for translation of 2 large replicative proteins pp1a and pp1b. Expression of these large polyproteins causes ribosomal frameshifting of upstream translation termination codon.[8] Their continued synthesis and subsequent cleavage by proteinases yield membrane-bound replicase complex. This complex mediates both genomic replication and transcription of subgenomic mRNAs. These mRNAs translate structural and nonstructural proteins of the virus, which are assembled in endoplasmic reticulum and Golgi complex. These virions are subsequently released out of cell by exocytosis.[9] This repeated cycle of cellular entry and exit infects adjacent pneumocytes and causes pneumonia (pulmonary phase) and subsequent systemic organ involvement. Few patients may have a phase of exuberant inflammatory response with cytokine storm. Drugs

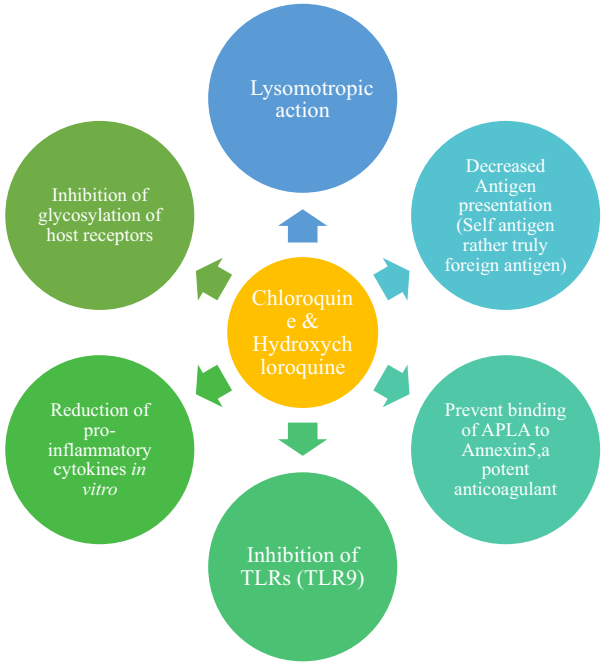

Figure 3 Antiviral and immunomodulatory effects of chloroquine and hydroxychloroquine. TLR, toll-like receptor.

Table 3 Clinical Studies Other Than Hydroxychloroquine in Patients With COVID-19.

Authors	Type of study (No. of patients)	Treatment arms	Study population (Prior treatment)	Virologic outcomes	Clinical outcomes	MV	Serious adverse events	Death	Comments
Cao B *et al.* Mar 2020, China[23]	Open label RCT (1:1) (n = 199)	Lopinavir-ritonavir (400/100 mg 12hrly) x 14 d vs Standard of care	Severe COVID-19: (O_2 sat <94%, PaO_2: FiO_2 <300) (11% on INF treatment)	No difference in viral loads over time or as per disease severity	No difference in clinical improvement (HR 1.31)	30.7% on MV and 2% on ECMO	20% (GI AEs more common, 13.8% discontinued)	19.2% vs 25%	No significant difference i n RNA negativity, clinical outcome or mortality
Grein J *et al.* Apr 2020, (US, Europe, Japan)[24]	Compassionate use study (n = 53)	Remdesivir 200 mg IV D1, 100 mg IV D2-10. No control arm	Severe COVID-19: (O_2 sat <94%, PaO_2: FiO_2 <300) (Treatment naöve)	NR	Clinical improvement in 68%, Extubation 57%, Discharge 47%	57% on MV and 8% on ECMO	23% (LFT abnormality 23%, 8% discontinued)	13%	No virologic data, no control arm, significant clinical improvement
Wang Y *et al.* Apr 2020, China[25]	RCT (2:1) (n = 237)	Remdesivir 200 mg IV D1, 100 mg IV D2-10 vs Placebo controlled arm	Severe COVID-19: (O_2 sat <94%, PaO_2: FiO_2 <300 and pneumonia) (LPV/RTV, INF, Steroids)	No significant reductions in viral load	No difference in time to clinical improvement (HR 1.23)	16% on MV and 1% on ECMO	18% (12% discontinued)	14%	No difference in viral or clinical outcomes including mortality
Beigel JH *et al.* May 2020, USA[26]	Double blind, RCT (1:1) (n = 1063)	Remdesivir 200 mg IV D1, 100 mg IV D2-10 vs Placebo controlled arm	Hospitalized patients with lower respiratory t ract infection	NR	Shortened time to recovery (11 d vs 15 d)	25.6%	21.1%	7.1% at D14	Ill defined patient population, virologic outcomes not reported, modest benefit in patients who were not on mechanical ventilation
Goldman JD *et al.* May 2020, USA[27]	Open-label, RCT (1:1) (n = 397)	Remdesivir 200 mg IV D1, 100 mg IV D2-5 vs Remdesivir 200 mg IV D1, 100 mg IV D2-10	Severe COVID-19: (O_2 sat <94%, and pneumonia); excluded patients on mechanical ventilation	NR	Clinical improvement in 64% vs 54% at D14	None	21% vs 35%	8% vs 11%	Lack of placebo arm, virologic outcomes not reported, cannot be extrapolated to critically ill patients

(*Continued on next page*)

Table 3 (*Continued*)

Authors	Type of study (No. of patients)	Treatment arms	Study population (Prior treatment)	Virologic outcomes	Clinical outcomes	MV	Serious adverse events	Death	Comments
Cai Q *et al.* Mar 2020, China[28]	Prospective, open-label non-RCT (n = 80)	Oral FPV (D1: 1600 mg 12hrly; D2-14: 600 mg 12hrly) plus IFN-α inhalation (n = 35) vs LPV/RTV (D1-14: 400 mg/100 mg 12hrly) plus IFN-α inhalation (n = 45)	Excluded Severe COVID-19 (Treatment naöve)	Shorter viral clearance time (4 d Vs 11 d)	Significant improvement in chest imaging (91.43% vs 62.22%)	None	11.4%	None	Excluded severe disease, only radiological outcomes defined
Chen C *et al.* Mar 2020, China[29]	RCT (1:1) (n = 240)	Favipiravir (D1: 1600 mg 12hrly; D2-10: 600 mg 12hrly) vs Umifenovir (Arbidol) (200 mg 8hrly) for 10 days	Chinese definition of COVID-19 pneumonia (PCR + rate: approx. 42%, Severe disease only in 11%, treatment naöve)	NR	Quicker relief from fever and cough, no difference in clinical recovery, oxygen support or non-invasive ventilation	None	32% vs 23%	NR	No difference in ICU admission, oxygen support, respiratory failure or mortality
Luo P *et al.* Mar 2020, China[31]	Observational study (n = 15)	Tocilizumab (80–600 mg/dose); 5 received >/ = 2 doses No control arm	87% serious disease, CRP >5.0 mg/L; IL-6 >7.0 pg/mL	NR	Clinical stabilization 60%, clinical improvement 7%, disease aggravation 13%	NR	NR	20%	Small sized and ill-defined study population, no discrete clinical outcomes
Alattar R *et al.* May 2020, Qatar[32]	Observational study (n = 25)	Tocilizumab median total dose was 5.7 mg/kg (range 3.7–20 mg/kg) No control arm	Severe COVID-19: (RR > 30/min, O_2 sat <93%, PaO_2: FiO_2 <300 and pneumonia) With raised CRP (HCQ, AZT, LPV/RTV, INF, RBV)	NR	Rapid decline in fever and CRP levels, radiological improvement in 68% at D14, weaning off from invasive ventilation at D14 > 50%, Discharge 36%	84%	92% at least one AE	12%	IL-6 levels not measured, no fixed dosage of Tocilizumab, confounders like concomitant multiple interventions

Table 3 (*Continued*)

Authors	Type of study (No. of patients)	Treatment arms	Study population (Prior treatment)	Virologic outcomes	Clinical outcomes	MV	Serious adverse events	Death	Comments
Shen C *et al.* Mar 2020, China[34]	Observational study (n = 5)	Convalescent plasma transfusion (SARS-CoV-2–IgG binding titer >1:1000 and neutralization titer >1:40)	Critically ill COVID-19 and ARDS (Antivirals and steroids)	Viral clearance by D12	Resolution of ARDS and weaning from ventilator 80%, Discharge 60%	All	NR	None	Increase in neutralizing antibody titers, improvement in clinical status
Duan K *et al.* Apr 2020, China[35]	Observational study (n = 10)	Convalescent plasma transfusion (SARS-CoV-2–IgG neutralization titer >1:640)	Severe COVID-19 and pneumonia (Antivirals and steroids)	Viral clearance in all (7/7)	Improved oxygen status 30%, stable 70%, discharge 30%	30%	None	None	Trend toward clinical, radiological and biochemical improvement

Abbreviations: AE, adverse events; ARDS, acute respiratory distress syndrome; AZT, azithromycin; CQ, chloroquine; COVID-19, COrona VIrus Disease-2019; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; GI, gastro-intestinal; HCQ, hydroxychloroquine; HR, hazard ratio; IL-6, interleukin-6; INF, interferon; LFT, liver function test; LPV/RPV, lopinavir/ritonavir; MV, mechanical ventilation; NR, not reported; RBV, ribavirin; RCT, randomized control trial; RR, respiratory rate.

acting at different stages of viral lifecycle and disease phases have been summarized in Table 1.

TREATMENT

There is no approved treatment for SARS-CoV-2 at present, and the current guidance is from previous treatment experiences of 2003 Severe Acute Respiratory Syndrome (SARS) and 2015 Middle East Respiratory Syndrome (MERS) outbreaks. Few drugs like chloroquine (CQ), remdesivir, and favipiravir have shown *in vitro* activity against SARS-CoV-2 and have been re-purposed for its treatment. Immunomodulatory therapies (i.e. interlukin-6 inhibitors) have been proposed for patients with hyperinflammatory response and convalescent plasma treatment for severe COVID-19 with multiorgan dysfunction. We briefly review and critically analyze the clinical experience with these treatment modalities, as of June 12, 2020.

CHLOROQUINE AND HYDROXYCHLOROQUINE

CQ and HCQ are structurally similar weak lipophilic bases with a hydroxyethyl group in HCQ in place of ethyl group of CQ. They are widely used in the treatment of malaria and other inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus. *In vitro* studies using Vero cells have efficacy of CQ and HCQ against SARS-CoV-2. HCQ was seen to be more potent than CQ. Based on the pharmacologic properties, loading dose of 400 mg HCQ twice daily followed by 200 mg twice daily for 4 days was suggested.[10]

Proposed antiviral and immunomodulatory actions of these drugs include lysosomotropic property, prevention of the conversion of toxic heme into non-toxic hemozoin (antimalarial activity), inhibition of glycosylation of host receptors, reduction of pro-inflammatory cytokines, reduced TNF-α production by activated macrophages, reduced expression of TNF-α receptors on monocytes, inhibition of toll-like receptors, inhibition of various processes in innate and adaptive immunity (immunoregulatory effect), decreased antigen presentation, and prevention of binding of anti-phospholipid antibodies (APLA) to Annexin5 which is a potent anticoagulant (Figure 3). Both CQ and HCQ are weak bases and get concentrated in acidic organelles such as endosomes, golgi, and lysosomes. They increase intracellular pH, disrupt enzymatic processes, and cause cellular dysfunction. CQ and HCQ decreases intracellular iron by increasing endosomal pH and further impairing endosomal release of iron from transferrin. This change in iron levels also causes dysfunction of several intracellular enzymes involved in DNA replication. Thus, CQ and HCQ prevent cellular entry of enveloped viruses *via* endosomal

routes along with impairment of late stages of viral replication.[11,12]

In February 2020, Gao *et al.* published first experience from China of more than 100 patients treated with chloroquine.[13] They concluded that CQ is superior to control in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting virus negativity, and shortening the disease course. Based on this experience, it was recommended for treatment in the next set of guidelines issued by the National Health Commission of the People's Republic of China. However, no details regarding CQ dosage, characteristics of study population, or outcomes were provided to draw any meaningful conclusions (Table 2).[14] Chen *et al.* in a subsequent randomized control trial (RCT) from China had shown that there was no significant change in viral negativity and clinical outcomes in 30 patients of mild COVID-19 treated with HCQ.[15] Another RCT of 62 patients from China by Chen *et al.* showed significant improvement in time to clinical recovery (fever and cough remission) and improved pneumonia (80.6% vs 54.8%) in patients treated with HCQ. Virologic outcomes were not assessed in this study.[16]

Three studies were reported from France which studied role of HCQ and azithromycin in patients with mild COVID-19 (Table 2). Gautret *et al.* in a small cohort of 42 patients reported viral negativity in nasopharyngeal swab at Day 6 in all patients treated with HCQ and azithromycin combination versus 57.1% in patients receiving HCQ alone versus 12.5% in control arm. No clinical outcomes were reported.[17] In an extension of this cohort, the same group subsequently reported experience of 80 patients with viral negativity in nasopharyngeal swab (83% negative at Day 7, 93% at Day 8) and in viral cultures (97.5% at Day 5). Majority of patients (81.2%) were discharged after median 5 days of hospitalization with 1 death.[18] However, these virologic outcomes were not replicated by Molina *et al.* from France in which 80% nasopharyngeal swabs were positive at Day 5–6 in a small cohort of 11 patients.[19]

In a largest observational study from United States, Geleris *et al.* recently published their experience of HCQ in a cohort of 1446 patients with mild to severe COVID-19 (Table 2). Seventy patients who were intubated, died, or discharged within 24 h of admission and were excluded from analysis. Primary endpoint was respiratory failure which was a composite of intubation or death. In patients who died after intubation, primary endpoint was defined as time of intubation. Patients treated with HCQ had severe disease at baseline. Overall, 346 patients (25.1%) had a primary endpoint event. In unadjusted analysis, patients in HCQ arm had more primary endpoint events. However, propensity matched analysis showed no significant difference.[20]

Because these studies with CQ and HCQ have different therapeutic regimens, heterogenous study population, unequal arms to compare, ill-defined outcomes, and nonreproducible results, further randomized trials are needed before recommending the routine use of HCQ in mild COVID-19. Recently, a large multinational registry analysis failed to show benefits of HCQ in COVID-19, which was later retracted because of inconsistencies in data set, and the analysis that was conducted.[21]

Boulware *et al.* published a randomized trial of HCQ on postexposure prophylaxis of COVID-19 in 821 asymptomatic participants. There was no significant difference in incidence of new COVID-like illness across both arms (11.8% versus 14.3%). Adverse events were more common in HCQ arm as compared with placebo (40.1% vs 16.8%). Although recommended by many government authorities worldwide, benefits of HCQ as prophylactic agent are not clear as of now.[22]

LOPINAVIR/RITONAVIR

Lopinavir is a serine protease inhibitor, and ritonavir increases its plasma half-life by inhibiting CYP450. Cao *et al.* conducted open label RCT using lopinavir/ritonavir (LPV/RTV) in patients with severe COVID-19 (Table 3). Approximately, 31% patients of total 199 were on mechanical ventilation at baseline. The authors found no significant difference in viral loads over time or viral loads as per disease severity. Also, there was no significant difference in clinical outcomes and mortality in patients treated with LPV/RTV versus standard of care. Median time to clinical improvement was shorter by 1 day in LPV/RTV arm. Overall mortality was 22%. There was possible benefit of early intervention in a *post hoc* subgroup analysis. Patients who were treated within 12 days of symptom onset had a trend toward reduced mortality.[23]

REMDESIVIR

Remdesivir is a nucleotide analog and RNA polymerase inhibitor with *in vitro* activity against Ebola, SARS, MERS, and SARS-CoV-2. Grein *et al.* prospectively studied the role of remdesivir in a multicenter compassionate use study in patients with severe COVID-19. Of 61 patients, 57% were on mechanical ventilation at baseline (Table 3). Thirty-six patients (68%) had an improvement in oxygen-support class over a median follow-up of 18 days. A total of 25 patients (47%) were discharged, and 7 patients (13%) died. Cumulative incidence of clinical improvement was higher in patients on non-invasive ventilation at baseline versus invasive ventilation. When stratified by age, clinical improvement was lower in patients with >70 years of age compared with 50–70 years of age and highest in <50 years of age.[24]

In a double blind, placebo-controlled RCT, Wang *et al.* studied the role of remdesivir in 237 patients with severe

COVID-19 pneumonia (Table 3). Concomitant use of lopinavir–ritonavir, interferons, and corticosteroids were allowed. Authors found no significant difference in time to viral clearance, time to clinical improvement, or mortality across both the groups. Patients who had symptom duration of 10 days or less had numerically faster time to clinical improvement. Overall mortality was 14%.[25]

In a recent double-blind, placebo-controlled, multinational RCT, Beigel *et al.* studied role of remdesivir in 1063 hospitalized patients with COVID-19 and lower respiratory tract infections (Table 3). They found improved time to recovery (11 days vs 15 days) in remdesivir arm. In this study, 83.7% patients were on supplemental oxygen therapy including non-invasive and invasive mechanical ventilation. Mortality in remdesivir arm was 7.1%. Remdesivir improved outcomes mostly in patients requiring supplemental oxygen; there was no change in outcome in patients who were already on mechanical ventilation. This preliminary analysis included a heterogenous population of moderate to severe disease, and previous treatment status and virologic outcomes are not reported.[26]

In another open-label, multinational RCT, Goldman *et al.* studied 5-day versus 10-day remdesivir in 397 patients with COVID-19 requiring supplemental oxygen (Table 3). Patients requiring mechanical ventilation were excluded at baseline. There was no significant difference in clinical recovery across both the arms. In multivariate analysis, age < 65 years, baseline low oxygen requirement, and no biologic medication were associated with shorter time to clinical improvement.[27]

These 4 clinical studies on remdesivir had heterogenous population at baseline with different disease severity, nonuniform reporting of virologic outcomes, and differently defined clinical outcomes. Large multicenter RCTs with well-defined population at baseline which show virologic, clinical, radiological, and mortality improvements are the need of hour. With the current evidence, remdesivir improves clinical outcomes when given early during moderate to severe disease.

FAVIPIRAVIR

Favipiravir is a purine nucleotide with *in vitro* activity against SARS-CoV-2. It is approved for the treatment of influenza in Japan. In an open label control study from China involving 80 patients without severe COVID-19, Cai *et al.* compared favipiravir with inhalational interferon-α (INF-α) against LPV/RTV with inhalational INF-α (Table 3). Authors found better therapeutic responses in favipiravir arm with early radiological resolution of pneumonia and shorter time to viral clearance. No clinical outcomes were reported in this study.[28]

Umifenovir (Arbidol) acts by inhibiting the membrane fusion of viral envelope. It is approved for treatment of influenza in Russia and China. Chen *et al.* studied favipiravir versus arbidol in a prospective RCT comprising of 240 patients. Patients were included as per Chinese definition of COVID-19 pneumonia with only 42% nasopharyngeal swab positivity at inclusion. Severe disease was present only in 11% of total patients. Authors found quicker relief from fever and cough in favipiravir arm. There was no difference in need of auxiliary oxygen therapy or non-invasive mechanical ventilation. Virologic outcome was not assessed.[29]

TOCILIZUMAB

Tocilizumab (TCZ) is a monoclonal antibody against interleukin-6 (IL-6) and has been used in patients with inflammatory disorders like Juvenile rheumatoid arthritis and Crohn's disease. TCZ inhibits IL-6 receptors (IL-6R) and reduces the inflammatory milieu including acute phase reactants like C-reactive protein (CRP). There is transient elevation in serum levels of IL-6 and soluble IL-6R (sIL-6R) after TCZ administration. It is suggested that TCZ forms immune complexes with sIL-6R, thereby increasing elimination half-life of sIL-6R. Free IL-6 levels are increased because IL-6R–mediated consumption of IL-6 is inhibited by the unavailability of TCZ-free IL-6R as long as TCZ is available in circulation. Increased level of free IL-6 during TCZ treatment closely reflects the actual endogenous IL-6 production and true disease activity. If the basic cause of IL-6 overproduction is addressed, IL-6 levels should subsequently decrease by natural degradation.[30]

Luo *et al.* used TCZ in 15 patients (87% with severe disease) of COVID-19 who had raised CRP (>5.0 mg/L) and IL-6 (>7.0 pg/mL) at baseline. TCZ was given at (80–600 mg/dose); 5 patients received ≥2 doses of TCZ. Eight patients also received steroids. There was rapid decrease in CRP in all patients. Serum IL-6 level initially spiked and then decreased after TCZ therapy in 10 patients. A persistent and dramatic increase of IL-6 was observed in 4 patients who had treatment failure. Three patients died, 2 had disease aggravation, 1 had clinical improvement, and 9 had clinical stabilization after TCZ therapy. Virologic data were not assessed in the study.[31]

Recently, Alattar *et al.* published their experience with TCZ in 25 patients with severe COVID-19 from Qatar. All patients had received at least 2 concomitant investigational antivirals before TCZ. IL-6 levels and viral loads were not measured. There was significant reduction in CRP levels after TCZ therapy; median CRP was 193 mg/L on Day 1, 7.9 mg/L on Day 3, and <6 mg/L on Day 7. Radiological improvement was seen in 68% patients at Day 14. Proportion of patients who were on invasive

ventilation at the time of TCZ initiation decreased from 84% to 60% on Day 7 and 28% on Day 14. Nine patients (36%) were discharged and three (12%) died.[32]

CONVALESCENT PLASMA TRANSFUSION

The US FDA has issued guidance for use of investigational COVID-19 convalescent plasma in patients with laboratory confirmed severe or immediately life-threatening COVID-19. They recommended neutralizing antibody titers of at least 1:160 against SARS-CoV-2.[33] Shen *et al.* first reported their experience of convalescent plasma therapy in 5 critically ill patients COVID-19 and acute respiratory distress syndrome (ARDS) (Table 3). Convalescent plasma used had SARS-CoV-2 IgG binding titer >1:1000 and a neutralization titer >1:40. All patients had received antivirals and steroids until the SARS-CoV-2 viral loads became negative. Transfusion of convalescent plasma was shown to be associated with normalization of body temperature, increase in pO_2/FiO_2, and decrease in Sequential Organ Failure Assessment (SOFA) score. Viral clearance was seen in all 5 patients by Day 12. Resolution of ARDS with subsequent weaning was seen in 4 patients by Day 12. There was no mortality reported; 3 patients were discharged, and 2 remained stable at Day 37. There was improvement in neutralizing antibody titer from 40–60 to 80–320 by Day 7.[34]

Subsequently, Duan *et al.* reported their experience of 10 patients with severe COVID-19 pneumonia treated with convalescent plasma. Convalescent plasma used had SARS-CoV-2 neutralizing antibody titer >1:160. Plasma transfusion was well tolerated with maintenance of antibody titers and clearance of viremia by Day 7. There was no mortality, and trend toward clinical, radiological, and biochemical improvements.[35]

There is no approved treatment of SARS-CoV-2 at present. With elucidation of viral genome, combination of newer drugs with proven activity at different stages (like polypeptide synthetase inhibitors, replicase inhibitors) of SARS-CoV-2 lifecycle and disease pathogenesis may pave the way for viral elimination. With the available evidence so far, HCQ may be used as prophylaxis in high-risk individuals with unproven benefits. No recommendation regarding use of HCQ in treating COVID-19 can be made at present. Because favipiravir and lopinavir-ritonavir did not provide significant benefits in viral clearance or clinical improvement in severe disease, further randomized trials are necessary before recommending these drugs in clinical practice. Remdesivir improves clinical outcomes when given early during moderate to severe disease and should be strongly considered. TCZ has been found useful in patients with cytokine storm and elevated IL-6 levels. Convalescent plasma transfusion can be used as rescue therapy in critically ill COVID-19 pneumonia as a part of clinical trials. A suggested algorithm would be to categorize patients into low-risk and high-risk group at presentation. Remdesivir ± TCZ should be used early in the disease course, before multiorgan dysfunction sets in. Convalescent plasma can be used as rescue therapy in patients with multiorgan dysfunction. Further multicenter randomized trials are necessary for proving the benefit of these available, re-purposed drugs until newer drugs are available.

CONFLICTS OF INTEREST

The authors have none to declare.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Swapnil Dhampalwar: Writing - original draft, Formal analysis, Writing - review & editing. **Sanjiv Saigal:** Conceptualization, Writing - review & editing, Supervision. **Arvinder S. Soin:** Writing - review & editing, Supervision.

REFERENCES

1. World Health Organization. *WHO Emergencies Coronavirus Emergency Committee Second Meeting*. 2020 Jan.
2. Ramakrishna G, Kumar P, Aggarwal S, et al. SARS-Cov-2 (human) and COVID-19: primer 2020. *Hepatol Int*. 2020;2:2–4 (0123456789).
3. Gorbalenya AE, Baker SC, Baric RS, et al. The species and its viruses – a statement of the Coronavirus Study Group. *Biorxiv (Cold Spring Harb Lab [Internet]*; 2020:1–15. Available from: https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1.full.
4. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU); https://coronavirus.jhu.edu/map.html.
5. Rhoades A. *U.S. Department of Health and Human Services*. vol. 564. 2020:1–6 https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidtherapeutics.
6. Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect*. 2020;26:729–734.
7. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. *Diabetes Metab Syndr*. 2020 Apr 18;14:407–412. https://doi.org/10.1016/j.dsx.2020.04.020. Epub ahead of print. PMID: 32335367; PMCID: PMC7165108.
8. Thiel V, Ivanov KA, Putics Á, et al. Mechanisms and enzymes involved in SARS coronavirus genome expression. *J Gen Virol*. 2003;84:2305–2315.
9. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA, J Am Med Assoc*. 2020;2019.
10. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory Syndrome main point : hydroxychloroquine was found to be more potent than chloroquine at inhibiting SARS-CoV-2 in vit. *Clin Infect Dis*. 2020;2:1–25.
11. Katz SJ, Russell AS. Re-evaluation of antimalarials in treating rheumatic diseases: Re-appreciation and insights into new mechanisms of action. *Curr Opin Rheumatol*. 2011;23:278–281.

12. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis*. 2003;3:722–727.
13. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14:1–2.
14. Taccone FS, Gorham J, Vincent J-L. Hydroxychloroquine in the management of critically ill patients with COVID-19: the need for an evidence base. *Lancet Respir Med*. 2020;2:2019–2021.
15. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ*. Mar 2020 https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.
16. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv [Internet]*. 2020;7, 2020.03.22.20040758. Available from: http://medrxiv.org/content/early/2020/04/10/2020.03.22.20040758.abstract%0Ahttps://www.medrxiv.org/content/medrxiv/early/2020/04/10/2020.03.22.20040758.full.pdf.
17. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents [Internet]*. 2020:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949. Available from:.
18. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Travel Med Infect Dis [Internet]*. 2020 Apr:101663. https://doi.org/10.1016/j.tmaid.2020.101663. Available from:.
19. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Maladies Infect [Internet]*. 2020:2–3. https://doi.org/10.1016/j.medmal.2020.03.006. Available from:.
20. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with covid-19. *N Engl J Med*. 2020:1–8. https://doi.org/10.1056/NEJMoa2012410.
21. Mehra MR, Ruschitzka F, Patel AN. Retraction - hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet (London, England) [Internet]*. June 4 2020 https://doi.org/10.1016/S0140-6736(20)31324-6. Published Online.
22. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for covid-19. *N Engl J Med [Internet]*; 2020:1–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32492293.
23. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. *N Engl J Med*. 2020;1–13.
24. Grein J, Ohmagari N, Shin D, et al. Compassionate use of Remdesivir for patients with severe covid-19. *N Engl J Med*. 2020;1–10.
25. Wang Y, Zhang D, Du PG, et al. Articles Remdesivir in adults with severe COVID-19 : a randomised. *Lancet [Internet]*. 2020;6736:1–10. https://doi.org/10.1016/S0140-6736(20)31022-9. Available from:.
26. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of covid-19 - preliminary report. *N Engl J Med [Internet]*; 2020:1–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32445440.
27. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in patients with severe covid-19. *N Engl J Med [Internet]*; 2020:1–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32459919.
28. Cai Q, Yang M, Liu D, et al. Experimental treatment with Favipiravir for COVID-19: an open-label control study. *Engineering [Internet]*. 2020:4–10. https://doi.org/10.1016/j.eng.2020.03.007 (xxxx): Available from:.
29. Chen C, Huang J, Cheng Z, et al. Favipiravir versus Arbidol for COVID-19: a randomized clinical trial. *medRxiv*. 2020, 2020.03.17.20037432.
30. Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. *Blood*. 2008;112:3959–3964.
31. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol*. 2020 Mar:1–5.
32. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe COVID-19. *J Med Virol*. 2020 https://doi.org/10.1002/jmv.25964. Accepted Author Manuscript.
33. Food T. *Revised Information for Investigational COVID-19 Convalescent Plasma*. vol. 2. 2020:1–4 https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma.
34. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA, J Am Med Assoc*. 2020;323:1582–1589.
35. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci*. 2020;117:202004168.