



Systematic Review on the Therapeutic Options for COVID-19: Clinical Evidence of Drug Efficacy and Implications

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Abstract: A novel coronavirus-2 (SARS-CoV-2) was first identified in Wuhan, China, and quickly spread globally. Several treatments have been proposed, many of which have proven ineffective. Consequently, there is a need to review the published evidence of drug clinical trials to guide future prescribing. A systematic review of published clinical trials and retrospective observational studies was carried out. The search was made using PubMed, Embase, MEDLINE, and China National Knowledge Infrastructure (CNKI) databases. Articles published between January 2020 and October 2020 and written in the English language were retrieved and included in the study. Researches that used traditional medicine, in-vitro and in-vivo animal studies, as well as reviews were excluded. Seventy-three relevant articles that fulfilled the inclusion criteria were finally selected and reviewed. Hydroxychloroquine, chloroquine, and azithromycin produced no clinical evidence of efficacy in randomized controlled clinical trials (RCT). However, retrospective observational studies reported the efficacy of remdesivir and lopinavir/ritonavir in reducing viral load, although there have been concerns with lopinavir/ritonavir and, more recently, remdesivir. Recently, tocilizumab, dexamethasone, and methylprednisolone significantly relieved lung inflammation and decreased mortality in patients with severe COVID-19. In addition, convalescent plasma was effective in boosting strong immunity among patients with mild COVID-19. There is currently no single worldwide approved therapeutic option for patients with COVID-19 despite the initial hype with medicines, including hydroxychloroquine. Nonetheless, dexamethasone has shown promise in symptomatic treatment and convalescent plasma in boosting immunity. New treatments are currently being researched, and the findings will be reported accordingly to provide evidence-based guidance for prescribers and policymakers.

Keywords: COVID-19, efficacy, remdesivir, hydroxychloroquine, dexamethasone, lopinavir/ritonavir, clinical-trials, therapeutic-option

Introduction

In December 2019, several cases of mysterious pneumonia with the severe acute respiratory syndrome (SARS) were first reported in Wuhan, China.^{1,2} A novel coronavirus 2 (SARS-CoV-2) was identified as the cause and later designated as COVID-19 by the World Health Organization (WHO).²⁻⁵ The disease's main symptoms include fever, cough, shortness of breath, and fatigue. Other symptoms comprise sore throat, headache, myalgia, chills, nasal congestion, conjunctivitis, and diarrhea.²⁻⁶ Vital co-morbidities associated with death to COVID-19 include hypertension, diabetes, coronary heart disease, cerebral infarction, severe asthma,

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pneumonia, and chronic bronchitis.^{5,7–13} In addition, death due to COVID-19 is associated with several disease symptoms. Prominent among them include chronic pneumonia, which causes severe respiratory distress, sepsis-associated organ failure, and high D-dimer levels, which indicate the high risk of deep vein thrombosis. Also, elderly patients may experience widespread inflammation and suppression of body defense mechanisms, making them vulnerable to opportunistic infections.^{5,14} Ethnicity may also play a role as seen, for instance, in the United Kingdom and the USA; however, the exact reasons underlying the early observations are uncertain.^{7,15,16} Furthermore, SARS-CoV-2 infection appeared to produce a lesser fatality rate (3.1%) than previous SARS-CoV-1 (9.6%) and the Middle East respiratory syndrome (MERS-CoV) (34.4%).^{1,3,17} The novel SARS-CoV-2 is believed to invade a host's cell and initiate disease through binding to the angiotensin-converting enzyme-2 receptor (ACE-2 receptor).^{18–20} As such, an *ACE-2* gene is considered responsible for coding genetic information for the expression of the ACE-2 receptor for both coronavirus 1 and 2.^{18–21} Consequently, a higher expression of the ACE-2 receptors increases the risk of COVID-19 infections. Furthermore, some ACE-2 variants genes could reduce the association between ACE-2 receptors and spike-protein of the coronavirus. Therefore, altering this gene could significantly affect the expression pattern of the human ACE-2 receptor in different cells and tissues, which appears critical for the susceptibility, symptoms, and outcome of COVID-19 infection.^{18,19} Patients on angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) are associated with a considerably low risk of COVID-19 infection. This is because ACEI stalls angiotensin's activity, converting enzymes linked to COVID-19 ACE-2 receptors, reducing the cell invasion. Equally, ARBs pre-occupy the COVID-19 ACE-2 receptors, thus minimize the interaction between the coronavirus and the host's cells. Moreover, a report showed that COVID-19 patients on ACEI or ARBs had decreased the need for ICU admission.²² However, the findings vary according to several issues, including the study population.²³

A COVID-19 suspected patient is generally diagnosed using a reverse transcriptase-polymerase chain reaction (RT-PCR) assay, with a nasal swab or broncho-alveolar lavage fluid as test-specimens.^{24–26} Other methods of COVID-19 detection include radiologic imaging or chest X-ray that are frequently employed to detect lung damage. Also, enzyme-linked immunoassays (ELISA), lateral flow

immunoassays (LFIA), neutralization assays, and chemiluminescent assays are required COVID-19 testing methods.^{24–26} COVID-19 patients are considered to have severe pneumonia, which may require a ventilator if they are experiencing respiratory distress (≥ 30 breaths per min); oxygen saturation at rest ($\leq 93\%$); a ratio of the partial pressure of arterial oxygen to fractional oxygen concentration ($\text{paO}_2/\text{fiO}_2$) ≤ 300 mm hg; or having severe complications such as organ failures.^{27,28} Lung inflammation, an essential symptom of severe pneumonia, occurs with baseline fever ($>38^\circ\text{C}$), C-reactive protein (10 times than usual 5 mg/dl), ferritin (2 times of 400 $\mu\text{g/l}$), or IL-6 (10 times than 3.4 mg/l).^{27,28} The goal of managing patients with COVID-19 infection is to reduce the viral load, improve lung function, treat any fever, control diarrhea, and improve the body's immune system, known as the standard of care (SOC).^{27,28} Some medicines that have been prescribed for patients with COVID-19 include antiviral agents (lopinavir 40 mg/ritonavir 100 mg twice a day or remdesivir 100 mg/day), antibiotics including azithromycin (500mg daily) and ceftriaxone (1g daily), antimalarials, including hydroxychloroquine (600mg daily), zinc sulfate (20mg daily), dexamethasone (6mg/day), and vitamin C (3g daily).^{27,29–38}

Recently, there have been concerns over several recommended medicines. Prominent among them is hydroxychloroquine (HCQ), with the concerns of lack of a control arm in the initial trials leading to the hype, adverse reactions, and suicides.^{30,31,39–43} Subsequent studies typically failed to show any clinical benefit from HCQ prescribing alongside potential harm resulting in the WHO dropping HCQ from its current global studies.^{31,44–50} Lopinavir/ritonavir treatments have also been dropped by the WHO based on concerns of lack of efficacy.^{44,51} This has prompted the need to try other potential medicines to treat patients with COVID-19. This is because preventative measures such as lockdowns, social distancing, frequent hand washing, track and trace systems, and closing of borders have resulted in unintended consequences.^{29,52–58} African countries, including Botswana, Ghana, Uganda, and Asian countries including Korea, Malaysia, and Vietnam, are currently having comparatively low infection prevalence and mortality rates than high-income countries, including Italy, Spain, the United Kingdom, and the USA.^{17,29,59–69} Sequel to those concerns mentioned earlier, this review will focus on published clinical trials and retrospective observational studies for the therapeutic options of COVID-19 infection. We are

aware that there are several systematic and other reviews published already.^{31,33–35,37,46,70–84} However, we intended to build on this and analyze the most recent published papers to summarize some evidence-based therapeutic options for COVID-19 infection.

Materials and Methods

Data Sources

Data sources were four electronic databases, including PubMed, Embase, MEDLINE, and CNKI. The search terms used were clinical trials, evidence of efficacy, COVID-19, drug treatment, randomized, double-blinded, controlled trials, retrospective study, and therapeutic options.

Study Selection

The study was conducted according to the Prisma methodology for preferred reporting items for systematic reviews and meta-analyses, protocols 2015 (Prisma-p 2015).⁸⁵ Initially, 427 articles were retrieved from the databases on the therapeutic options for COVID-19 independently by the first two authors. After collecting the retrieved articles together, 136 duplicates were excluded. In addition, 183 articles were either in-vitro, in-vivo animal studies, or used medicinal plants, subsequently removed from collections. Afterward, 35 more articles were further excluded because they were either review or did not utilize an appropriate study design. Finally, 73 published articles that met the inclusion criteria were appraised in depth. This systematic review has included pre-printed publications where relevant as research on the COVID-19 Pandemic is a novel and evolving research area. The article retrieval, screening, and inclusion flow chart are shown in [Figure 1](#).

Inclusion Criteria

Studies published between January 2020 and October 2020 and written in the English language.

Exclusion Criteria

Studies undertaken using medicinal plants, in-vitro studies, in-vivo animal studies, and reviews.

Data Extraction

Published clinical trials and retrospective observational studies were selected. A further search was made to verify the articles' clinical trial registration number at www.clinicaltrials.gov, European clinical trial registry at <https://www.clinicaltrialsregister.eu/>, and Chinese clinical trial registry at <http://www.chictr.org.cn/searchprojen.aspx>.

The reference section of all the articles reviewed was used to generate additional relevant publications. There was also no attempt to assess the published papers' quality using scales such as the Newcastle Ottawa scale as some key papers are likely to be pre-publication.^{86–89}

Results

Our findings revealed a high degree of therapeutic failure among most of the medicines studied, building on recent NIH and WHO deliberations. The findings will be broken down by pertinent medicines starting with HCQ, with prospective and retrospective observational studies combined. Full details were depicted in [Tables 1 and 2](#).

Hydroxychloroquine (HCQ) with and without Azithromycin (AZM)

Hydroxychloroquine does not bind directly to the ACE-2 receptor for COVID-19 but acts by increasing the medium's acidity around which COVID-19 protein-spikes interact and bind ACE-2 receptors. The acidity will make the medium harsh, thereby degrading the viral spike and reducing the infection rate and spread of COVID-19.⁹⁰ Azithromycin directly blocks the binding of COVID-19 virus with ACE-2 receptors on the host's cell surface. Consequently, HCQ and AZM may have a place in the prophylaxis and treat patients with mild-moderate COVID-19 infections.⁹⁰ However, randomized controlled clinical trials (RCT) conducted in the United States and parts of Canada reported therapeutic failure of HCQ among 1309 COVID-19 asymptomatic patients.⁹¹ Similarly, HCQ did not produce better clinical outcomes than placebo among 30 treatment-naïve patients in China.⁹² In addition, HCQ failed to effectively treat 423 COVID-19 patients in a randomized, double-blind, placebo-controlled clinical trial conducted in Canada and the USA.⁹³ Other studies revealed therapeutic failure among 181 patients admitted to four different tertiary healthcare centers in France.⁹⁴ Alongside this, therapeutic failure was also seen among 293 patients with mild COVID-19 versus usual care.⁹⁵ Furthermore, HCQ, when combined with AZM, did not reduce mortality or the need for mechanical ventilation among COVID-19 patients enrolled in a randomized, controlled clinical trial in the USA.⁹⁶ Equally, HCQ combined with AZM did not

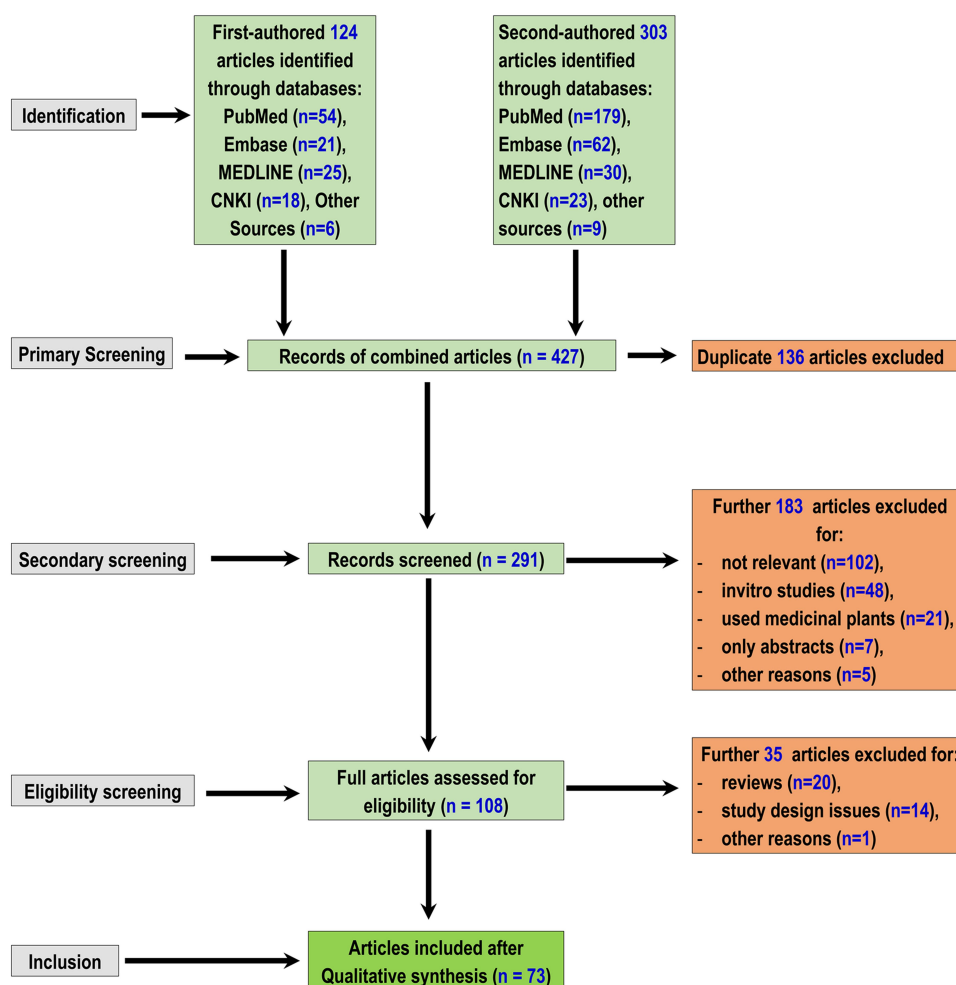


Figure 1 A Flow Chart Illustrating the Selection Process of Manuscripts.

produce better clinical outcomes among 504 COVID-19 patients versus standard care.⁹⁷ The UK recovery study involving 1542 patients randomized to HCQ compared with 3132 patients randomized to usual care showed no significant difference in 28-day mortality, duration of hospital stay, the need for mechanical ventilation, renal replacement, and development of major cardiac arrhythmias.⁹⁸

In an observational study involving 1376 consecutive patients in the USA, Geleris et al (2020) found that HCQ did not improve the outcomes using an endpoint of intubation of death versus non-HCQ patients.⁹⁹ In a large cohort study in the USA involving 3372 patients hospitalized with COVID-19, Singh et al (2020) demonstrated that HCQ did not confer any benefits to patients versus those who did not receive HCQ.¹⁰⁰ Ip et al (2020) in their study conducted in the USA involving 2512 patients also found no differences in mortality in patients prescribed HCQ with or without AZM versus patients receiving neither

therapy.¹⁰¹ In the treatment of COVID-19 using HCQ with or without AZM, patients' safety has been of great concern amplified by suicide attempts.^{41,102,103} In line with this, recent reviews indicated that HCQ causes neuropsychiatric side effects such as depression, psychosis, insomnia, manic episodes, and increased risk of suicide.^{104,105} In addition, more studies have reported adverse drug reactions associated with HCQ, especially prolongation of QTc (Corrected QT Interval). The QT interval is the time from the beginning of the QRS complex, representing ventricular depolarization, to the end of the T wave, resulting from the ventricular repolarization interval.^{48,49,91,106} However, Mahévas et al (2020) found that only 10% of patients experience electrocardiographic modifications requiring discontinuation of therapy.⁹⁴ Furtado et al (2020) found no therapeutic benefit in their open-label randomized trial involving 447 patients from adding AZM to HCQ.¹⁰⁷ Some of these findings might be explained because HCQ

Table 1 Evidence of Drugs Efficacy or Otherwise, from Clinical Trials

| S/N | Clinical Trial Identifier | Enrolment | Type of Treatment | Interventions | Study Design | Doses | Main Outcome | Reference |
|-----|---------------------------|-----------|--|--------------------------|--|---|--|------------------------------------|
| | NCT04304053 | 293 | Outpatients with mild to moderate COVID-19 | HCQ | Multicenter Open-Label, Randomized Controlled Trial | 800 mg on day 1, then 400 mg daily for 6-days | HCQ did not produce a better treatment outcome than standard care. | Mitija et al, 2020 ⁹⁵ |
| | ChiCTR2000029559 | 62 | Hospitalized patients with moderate COVID-19 | HCQ | Randomized, Double-Blind, Single-Center Trial | 400 mg on day 1, then 200 mg twice daily for 5-days | 80% of patients were relieved of pneumonia, fever, and cough | Chen et al, 2020 ¹⁵ |
| | NCT04261517 | 30 | Hospitalized patients with moderate COVID-19 | HCQ | Randomized, Single-Center Controlled Trial | 400 mg daily for 5-days | There was evidence of efficacy in a patient with moderate COVID-19 | Chen et al, 2020 ⁹² |
| | ChiCTR2000030054 | 67 | Hospitalized patients with moderate COVID-19 | 1. HCQ 2- Chloroquine | A Prospective Open-Label Randomized Controlled Study Single-Center | 1. CQ 1000 mg on day 1, Then 500 mg daily for 9-days 2.HCQ 200mg twice for 10-days | The CQ And HCQ showed efficacy in patients with moderate COVID-19 | Chen et al, 2020 ¹⁰ |
| | EuCTR.2020-000890-25. | 42 | Hospitalized patients with moderate COVID-19 | 1.HCQ 2. AZM | Open-Label, Non-Randomized, Clinical Trial | 1. HCQ 200 mg daily for 10- days 2. AZM 500 mg daily for 5- days | HCQ decreased viral load. AZM produced a synergistic effect | Gautret et al, 2020 ³⁰ |
| | NCT04308668 | 1309 | Prophylaxis | HCQ | Randomized, Double-Blind, Placebo-Controlled Multicenter Trial | 800 mg single dose, then 600 mg daily for 4- days | HCQ did not protect the patient from contracting COVID-19 | Boulware et al, 2020 ⁹¹ |
| | NCT04308668 | 423 | Outpatients mild COVID-19 | HCQ | Randomized, Double-Blind, Placebo-Controlled Trial | 800 mg once, then 600 mg 8 Hours later, 600 mg once daily for 4- days | HCQ did not significantly reduce the severity of the disease | Skipper et al, 2020 ⁹³ |
| | ChiCTR2000029868 | 150 | Hospitalized patients with severe COVID-19 | HCQ | Randomized, Open-Label, Multicenter Controlled Trial | 1200 mg daily for 3 days, then 800 mg daily for 2-weeks | Did not produce a significant negative conversion of COVID-19 patients | Tang et al, 2020 ⁰⁷ |

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Table 1 (Continued).

| S/ N. | Clinical Trial Identifier | Enrolment | Type of Treatment | Interventions | Study Design | Doses | Main Outcome | Reference |
|-------|-----------------------------|-----------|--|--|--|---|--|--------------------------------------|
| | NCT04384380 | 33 | Hospitalized patients with mild, moderate, and severe COVID-19 | HCQ | A Multicenter, Randomized, Open-Label, Controlled Trial | 400 mg twice on day 1, and 200 mg twice for 6-days | HCQ did not produce efficacy in subjects with mild to moderate COVID-19. | Chen et al, 2020 ¹⁰⁸ |
| | R01ey028027 And R01ey029799 | 807 | Hospitalized patients with severe COVID-19 | 1. HCQ 2. AZM | Prospective Randomized, Open-Label, Multicenter Controlled Trial | 1. HCQ 400 mg twice daily for 5-Days 2. AZM 500 mg daily for 5-days | HCQ With AZM did not reduce mortality or need for mechanical ventilation | Magagnoli et al, 2020 ⁹⁶ |
| | NCT04322123 | 504 | Hospitalized patients with mild to moderate COVID-19 | 1. HCQ 2. AZM | Open-Label, Randomized Controlled Clinical Trial | 1. HCQ 400 mg twice for 7- days 2. AZM 500 mg daily for 7-days | HCQ alone or with AZM did not produce better treatment compared to standard care | Cavalcanti et al, 2020 ⁹⁷ |
| | NCT04280705 | 1062 | Hospitalized patients with moderate COVID-19 | Remdesivir | Randomized, Double-Blind, Placebo-Controlled Multicenter Trial | 200 mg single dose on day 1, then 100 mg daily for 9-days | Remdesivir shortened the time to recovery | Beigel et al 2020 ¹³⁷ |
| | NCT04292730 | 584 | Hospitalized patients with moderate COVID-19 | Remdesivir | Randomized, Open-Label Trial | 200 mg on day 1, then 100 mg/day for 4-days | Remdesivir was not effective alone compared to standard care | Spinner et al, 2020 ³⁸ |
| | NCT04257656 | 237 | Hospitalized patient with severe COVID-19. | Remdesivir | Randomized, Double-Blind, Placebo-Controlled Multicenter Trial | 200 mg on day 1, then 100 mg IV once daily for 9-Days | Remdesivir did Not significantly reduce time to recovery | Wang et al, 2020 ³² |
| | NCT04276688 | 86 | 1. Outpatients with mild COVID-19; 2. Hospitalized patients with moderate COVID-19. | 1. LPV/r 2. Interferon B-1b 3. Ribavirin | Randomized, Double-Blind, Controlled Multicenter Trial | 1. 400 mg/100 mg twice daily 2. Three doses of 8 million IU 3. 400 mg twice daily for 14-days | The triple combination effectively suppressed viral load and duration of hospital stay | Hung et al, 2020 ²⁰ |
| | ChiCTR2000029308 | 199 | Hospitalized patients with severe COVID-19 | LPV/r | Open-Label, Randomized Controlled Trial | 400 mg/100 mg twice daily for 14-days | No benefits were observed in patients with severe COVID-19 | Cao et al, 2020 ¹²³ |

| | | | | | | | |
|-------------------|-----|---|---------------------------------|---|---|--|--|
| NTC04252885 | 86 | Hospitalized patients with moderate COVID-19 | 1. LPV/r 2. Umifenovir | Exploratory Randomized Controlled Trial | 400/100 mg twice daily for 4-weeks | LPV/r or Umifenovir alone shows little benefit in COVID-19 patients | Li et al, 2020 ¹²⁴ |
| ChiCTR2000029600 | 80 | Hospitalized patients with moderate-severe COVID-19 | Favipiravir | An Open-Label Control Single-Centre Trial | FPV 1600 mg twice daily, then 600 mg twice daily for day 2–14 | Favipiravir produced faster recovery in COVID-19 patients than the control group | Cai et al, 2020 ¹²³ |
| JRCTs041190120 | 69 | Hospitalized patients with moderate COVID-19 | Favipiravir | A Prospective, Open-Label, Multicenter Trial | 1800 mg twice daily apart day 1, then 800 mg twice for 10 days | Favipiravir did not significantly improve COVID-19 viral clearance within 6 days | Doi et al, 2020 ¹²⁹ |
| NCT04434248 | 60 | Hospitalized patients with moderate COVID-19 | Favipiravir | A Prospective, Open Label, Randomized Multicenter -Clinical Trial | 1600mg twice day 1, then 600mg twice day 2–14 | Favipiravir significantly improve COVID-19 viral clearance within 5 days | Ivashchenko et al, 2020 ¹³⁰ |
| ChiCTR2000030254 | 240 | Hospitalized patients with severe COVID-19 | 1. Favipiravir 2. Umifenovir | Prospective Randomized, Open-Label, Multicenter Controlled Trial | 1. Favipiravir 1600 mg twice on day 1, then 600 mg twice daily for 10-days 2. Umefovir 200 mg three times daily for 7-days | FVR compared to Umifenovir did not significantly improve the patient's recovery | Chen et al, 2020 ¹²⁸ |
| ChiCTR20000300001 | 52 | Hospitalized patients with moderate COVID-19 | Triazavirin | A Pilot Randomized Multicenter Controlled Clinical Trial | Triazavirin 250 mg versus a placebo three or four times a day for 7- days | Triazavirin group required Fewer therapies for respiratory, cardiac, renal, hepatic, or coagulation supports | Wu et al, 2020 ¹³² |
| NCT04315480 | 100 | Hospitalized patients with severe COVID-19 | TCZ | Off-Label, Non-Randomized, Single-Center Study | TCZ 8mg/Kg twice daily IV | TCZ significantly reduced the need for mechanical ventilation, duration of hospital stays | Toniati et al, 2020 ¹⁵⁰ |
| | 63 | Hospitalized patients with severe COVID-19 | TCZ | A Prospective Open, Single-Arm Multicentre Trial | TCZ 8 mg/Kg IV or 324 mg SC | TCZ improve respiration in a patient with severe COVID-19 | Sciascia et al, 2020 ¹⁵¹ |
| NCT04346355 | 126 | Hospitalized patients with severe COVID-19 | TCZ | Prospective, Open-Label, Randomized Clinical Trial | TCZ 8 mg/Kg up to a maximum of 800 mg IV | TCZ did not improve disease progression compared with standard care | Salvarani et al, 2020 ¹⁶⁹ |

(Continued)

Table 1 (Continued).

| S/ N. | Clinical Trial Identifier | Enrolment | Type of Treatment | Interventions | Study Design | Doses | Main Outcome | Reference |
|----------|------------------------------|-----------|---|-----------------------------|--|---|---|---|
| | EudraCT 2020-001934-37 | 85 | Hospitalized patients with severe COVID- 19 | Methylprednisolone | Partially Randomized, Open-Label, Multicenter Controlled Trial | 400 mg twice daily for 3-days, then 20 mg twice daily for 3-days | The drug effectively reduced lung inflammation in a patient with severe COVID-19 | Corral et al, 2020 ⁴⁶ |
| | NCT04381936 | 6425 | Hospitalized patients with severe COVID- 19 | Dexamethasone | Open-Label, Double- Blind, Controlled Multicenter Trial | 6mg daily for 10-days | Dexamethasone significantly decreased the duration of hospital stay and mortality | Horby et al, 2020 ³⁶ |
| | NCT01731795 | 277 | Hospitalized patients with moderate-severe COVID-19 | Dexamethasone | Randomized, Multicenter Controlled Trial | 20 mg IV once daily for day 1-5, then 10 mg once daily for Day 6-10 | Early administration reduces the duration of mechanical ventilation, mortality | Villar et al, 2020 ⁴⁵ |
| | ChiCTR2000030046 | 10 | Hospitalized patients with moderate COVID-19 | Convalescent Plasma (CP) | Multicenter Open-Label, Randomized Trial | One-Dose of 200 mL of CP | CP neutralized COVID-19 and improve the clinical outcomes | Duan et al, 2020 ⁷¹ |
| | CTRI/2020/04/ 024775 | 464 | Hospitalized patients with moderate COVID-19 | Convalescent Plasma (CP) | Open-Label Multicentre Randomised Controlled Trial | Two doses of 200 mL CP; transfused 24 hours apart | CP did not reduce the disease progression and mortality. | Agarwal et al, 2020 ⁷⁵ |

Table 2 Clinical Evidence of Drugs Efficacy or Otherwise from Retrospective Observational Studies

| S/ N | Enrolment | Type of Treatment | Interventions | Study Design | Dose | Main Outcome | Reference |
|---------|-----------|--|----------------|---|--|--|------------------------------------|
| | 1067 | Outpatients with mild COVID-19 | HCQ | Retrospective Cohort, Observational Multi-Center Study | 600 mg/day | HCQ reduced the duration of hospital stay | Andrew et al, 2020 ¹¹¹ |
| | 3737 | Hospitalized patients with moderate COVID-19 | 1-HCQ 2-AZM | Retrospective Cohort Observational Study | 1. 200 mg three times daily for 10- days 2. 500 mg on day 1, then 250 mg daily for 4-days | HCQ-AZM treatment for at least 3 days decreased mortality and need for ICU | Lagier et al, 2020 ¹¹³ |
| | 2541 | Hospitalized Patients with severe COVID-19 | 1-HCQ 2-AZM | Retrospective Cohort, Observational Multi-Center Study | 1. 400 mg twice on day 1, then 200 mg twice daily for 5-days 2. 500 mg on day 1, then 250 mg daily for 4-days | HCQ, in combination with AZM, reduced the death rate in COVID-19 patients | Arshad et al, 2020 ¹¹⁴ |
| | 1061 | Hospitalized patients with moderate COVID-19 | 1-HCQ 2-AZM | A Retrospective Cohort, Single Centre Analysis | 1. 200 mg three times daily for 10- days 2. 500 mg Day 1, then 250 mg daily for 4-days | HCQ, combined with AZM, reduced mortality in patients with uncomplicated COVID-19. | Million et al, 2020 ¹¹⁶ |
| | 80 | Hospitalized patients with mild-moderate COVID-19 | 1-HCQ 2-AZM | Uncontrolled, Non-Comparative, Observational Cohort Study | 1. 400 mg twice daily for 5-days 2. 500 mg daily for 5-days | HCQ Combined with AZM Significantly reduced the Spread Of COVID-19 Infection. | Gautret et al, 2020 ¹¹⁷ |
| | 51 | Outpatients with mild/moderate COVID-19 | 1-HCQ 2-AZM | Retrospective Observational Study | 1. HCQ 600 mg daily for 7–10- days 2. AZM 500 mg on Day 1, then 250 mg daily for 4-Days | The combination of HCQ and AZM improved patients' recovery | Guérin et al, 2020 ¹¹² |
| | 1820 | Hospitalized patients with mild to moderate COVID-19 | HCQ | Retrospective Observational Multicenter Center Study | 400 mg twice on Day 1, and 200 mg twice for 6-Days | HCQ yield no significant benefit in subjects with COVID-19 | Singh et al, 2020 ¹⁰⁰ |
| | 1376 | Hospitalized patients with severe COVID-19 | HCQ | Retrospective, Observational Single-Center Study | 600 mg twice on Day 1, then 400 mg daily for four times a day | HCQ did not reduce the risk of intubation or fatality | Geleris et al, 2020 ⁹⁹ |

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Table 2 (Continued).

| S/N | Enrolment | Type of Treatment | Interventions | Study Design | Dose | Main Outcome | Reference |
|------|-----------|--|----------------------------|---|--|---|-----------------------------------|
| | 181 | Hospitalized patients with severe COVID-19 | HCQ | Retrospective, Observational Multicenter Study | 600 mg/Day | HCQ was not effective in patients with severe COVID-19 | Mahévas et al, 2020 ⁹⁴ |
| 37 | | Hospitalized patients with mild to moderate COVID-19 | HCQ | Retrospective Observational Study | 400 mg twice on day 1, and 200 mg twice for 6-days | HCQ did not produce efficacy in Patients with mild to moderate COVID-19 | Chen et al, 2020 ¹⁰⁸ |
| 2512 | | Hospitalized patients with moderate-severe COVID-19 | 1. HCQ 2. AZM 3. TCZ | Retrospective Cohort, Observational, Multicenter Study | 1. 400 mg loading dose then 200 mg twice daily for 5-Days 2. 500 mg daily for 5-days 3.8 mg/Kg | HCQ, in combination with AZM, did not increase survival. However, TCZ reduced mortality among ICU patients | Andrew et al, 2020 ¹¹¹ |
| 11 | | Hospitalized patients with severe COVID-19 | 1-HCQ 2-AZM | Prospective, Observational Single-Center Study | HCQ 600 mg/D for 10-days and AZM 500 mg day 1, then 250 mg for 5-days | HCQ combined with AZM produced no antiviral activity | Molina et al, 2020 ¹⁰⁹ |
| 61 | | Hospitalized patients with severe COVID-19. | Remdesivir | Prospective, Observational Cohort, Multi-Center Study | 200 mg loading dose on day 1, then 100 mg once daily for 9-days | There was faster recovery observed in 68% of patients | Grein et al, 2020 ¹³⁶ |
| 47 | | Hospitalized patients with moderate COVID-19 | LPV/r | A Retrospective Cohort Single Center Study | 400/100 mg twice daily for 4-weeks | LPV/r was effective against COVID-19 when combined with standard care | Ye et al, 2020 ¹²¹ |
| 33 | | Hospitalized patients with moderate COVID-19 | 1. LPV/r 2. Umifenovir | A Retrospective Cohort Single Center Study | 1.400/100 mg twice daily for 4-weeks 2. Umifenovir At 0.2g three times a day | LPV/r was effective when combined with Umifenovir | Deng et al, 2020 ¹²⁵ |
| 178 | | Hospitalized patients with moderate COVID-19 | 1. LPV/r 2. Umifenovir | A Retrospective Cohort Single Center Study | 1.400/100 mg twice daily for 4-weeks 2. Umifenovir At 0.2g three times a day | LPV/r and Umifenovir neither improved patients' health condition nor hastened negative conversion of COVID-19 | Wen et al, 2020 ¹²⁶ |
| 32 | | Hospitalized patients with moderate COVID-19. | LPV/r | Retrospective Cohort, Observational Single-Center Study | 400 mg/100 mg twice daily for 14- days | The drugs significantly reduced the duration of hospital stays with no mortality | Bowale et al, 2020 ¹²² |

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|------|---|---|---|--|---|---|
| 52 | Hospitalized patients with severe COVID-19 | 1. Oseltamivir, 2. Ganciclovir 3. LPV/r | A Single-Centered, Retrospective, Observational Study | Oseltamivir was given to 18 patients, Ganciclovir 14, and LPV/r seven patients | No efficacy produced in all groups | Yang et al, 2020 ¹²⁷ |
| 81 | Hospitalized patients with moderate COVID-19. | Umifenovir | A Retrospective Observational Cohort Study | Umifenovir at 0.2g three times a day | Umifenovir was not better than the control group in suppressing viral load | Lian et al, 2020 ¹³³ |
| 3924 | Hospitalized patients with severe COVID-19 | TCZ | A Retrospective Observational Cohort Multi-Center Study | 4-8 mg/Kg IV | TCZ decreased mortality at first 2 days of ICU admission compared to control group. | Gupta et al, 2020 ¹⁶² |
| 630 | Hospitalized patients with severe COVID-19 | TCZ | A Retrospective Observational Cohort Multi-Center Study | 4-8 mg/Kg IV | TCZ reduced mortality among COVID-19 patients requiring ICU | Biran et al, 2020 ¹⁵² |
| 544 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Cohort, Observational Multi-Center Study | 8 mg/Kg IV 2-times only in IV fluid | Reduce the risk of mechanical ventilation and death rate | Guaraldi et al, 2020 ¹⁵³ |
| 158 | Hospitalized patients with severe COVID-19 | TCZ | A Retrospective Cohort Observational Study | 400 mg first dose, then 400 mg after 24 hours | TCZ improved ventilation | De Rossi et al, 2020 ¹⁵⁵ |
| 154 | Hospitalized patients with moderate COVID-19 | TCZ | Retrospective Observational Study | 600 mg twice daily day-1, then 200 mg every 8 hours for 4-Days | TCZ significantly decreased mortality | Somers et al, 2020 ¹⁵⁶ |
| 104 | Hospitalized patients with severe COVID-19 | TCZ | Prospective, Observational, Single-Center Study | 8 mg/Kg | TCZ reduced requirement for ventilator and improved inflammatory biomarkers | Price et al, 2020 ¹⁵⁷ |
| 88 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Cohort, Observational Single-Center Study | 400 mg IV as hour infusion, 400 mg after 12 and 24 hours | TCZ was an effective immunomodulator in severe COVID-19 | Fernandez-Ruiz et al, 2020 ¹⁵⁸ |
| 77 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Cohort, Observational Single-Center Study | 4-8 mg/Kg | TCZ was associated with increased survival but a high risk of severe infections. | Moreno-Perez et al, 2020 ¹⁵⁴ |

(Continued)

Table 2 (Continued).

| S/ N | Enrolment | Type of Treatment | Interventions | Study Design | Dose | Main Outcome | Reference |
|---------|-----------|--|---------------------------------|--|--|--|---|
| | 45 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Case-Control Study | 4-8 mg/Kg | TCZ reduced the number of patients requiring ICU and death rate in patients with severe COVID-19 | Klopfenstein et al, 2020 ¹⁶¹ |
| | 21 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Observational Multicentre Study | 4-8 mg/Kg | TCZ improved clinical outcomes and reduced mortality in patients with severe COVID-19 | Xu et al, 2020 ²⁸ |
| | 15 | Hospitalized patients with moderate COVID-19 | TCZ | Retrospective, Observational Single-Center Study | 600 mg twice at a time | TCZ was effective in the treatment of Covid-19 patients with a risk of cytokine storms | Luo et al, 2020 ¹⁵⁹ |
| | 12 | Hospitalized patients with Severe COVID-19 | TCZ | Retrospective Cohort Observational Single-Center Study | 162 mg subcutaneously | TCZ improved lung function. | Mastroianni et al, 2020 ¹⁶⁰ |
| | 196 | Hospitalized patients with severe COVID-19 | 1. TCZ 2. Methylprednisolone | Off-Label Observational Single-Center Study | 1.8 mg/Kg IV 2. 1 mg/Kg for 5-days | Produced anti-inflammatory action and reduced negative impact of the immune response to COVID-19 | Mikulska et al, 2020 ²⁷ |
| | 112 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Cohort, Observational Study | 8 mg/Kg | TCZ did not reduce mortality or ICU admission | Colaneri et al, 2020 ¹⁴⁹ |
| | 66 | Hospitalized patient with severe COVID-19 | TCZ | Retrospective Cohort, Observational Single-Center Study | 8 mg/Kg, maximum of 800 mg per dose for 28-days | There was no efficacy in patients with severe COVID-19 | Knorr et al, 2020 ¹⁶⁴ |
| | 65 | Hospitalized patients with severe COVID-19 | TCZ | A Single-Centre Retrospective Cohort Observational Study | 400 mg first dose, then 400 mg after 24 hours as the second dose | No significant increase in recovery | Campochiaro et al, 2020 ¹⁶⁶ |
| | 51 | Hospitalized patients with severe COVID-19 | TCZ | Open-Label Prospective Observational Study | 400 mg first dose, then 400 mg after 24 hours as the second dose | No significant improvement in the patient's health condition | Morena et al, 2020 ¹⁶⁷ |
| | 51 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Cohort, Observational Single-Center Study | TCZ 4-8 mg/Kg, followed by adjunct treatment | TCZ showed no efficacy in patients with severe COVID-19 | Kewan et al, 2020 ¹⁶⁵ |

| | | | | | | | |
|--|-----|---|---|---|--|--|---|
| | 11 | Hospitalized patients with severe COVID-19 | TCZ | Retrospective Cohort Observational, Study | 600 mg twice daily on day 1, then 200 mg every 8 hours for 4- days | No improvement in the health condition of patients with severe COVID-19 | Rimland et al, 2020 ¹⁶⁸ |
| | 242 | Hospitalized patients with moderate COVID-19 | Methylprednisolone | An Observational Comparative Study | Methylprednisolone 250 mg daily for 3- consecutive days | Relieved inflammation and improved lung functions | Ruiz-Irastorza et al, 2020 ¹⁴⁷ |
| | 136 | Hospitalized patients with severe COVID-19 | 1. Methylprednisolone 2. Hydrocortisone 3. Dexamethasone 4. Prednisone | An Observational Cohort Analysis Of Dosing Patterns | | Early administration of corticosteroids improved survival in non-mechanically ventilated patients | Rahman et al, 2020 ¹⁴⁸ |
| | 49 | Hospitalized patients with severe COVID-19 | Convalescent Plasma (CP) | Prospective, Observational Multi-Center Study | One-dose of 200 mL of CP | CP was effective against COVID-19 if donors with the high level of SARS-CoV2 antibodies used early | Rasheed et al, 2020 ¹⁷² |
| | 25 | Hospitalized patients with severe COVID-19 | Convalescent Plasma (CP) | Retrospective Observational Single Center Study | 300 mL of CP for all | treatment with CP is safe and significantly improve the patients' health condition | Salazar et al, 2020 ¹⁷³ |
| | 50 | Hospitalized patients with moderate-severe COVID-19 | Anakinra | A Retrospective Cohort Single Center Study | Anakinra 5 mg/Kg twice a day IV or 100 mg twice a day SC | High-dose Anakinra was safe and showed efficacy against COVID-19 | Cavalli et al, 2020 ¹⁷⁷ |

did not appear to yield significant negative test results among 150 patients with mild to moderate COVID-19 versus standard care.¹⁰⁷ Another study involving 33 patients in an RCT and 37 in a retrospective study also failed to demonstrate that HCQ shortened viral shedding.¹⁰⁸ Molina et al (2020), in their initial study in France, also found no strong evidence of antiviral activity by HCQ.¹⁰⁹

In contrast, an initial trial in China involving 48 patients with moderate COVID-19 found that chloroquine (CQ) or HCQ showed a trend towards a decrease in the duration of hospital stay and lung computerized RCT.¹¹⁰ Andrew et al (2020) also reported that HCQ significantly reduced the duration of hospital stay in a retrospective observational study.¹¹¹ Guérin et al (2020), in their initial study in France involving 88 patients, also found that AZM plus HCQ favorably improved the patient's health status.¹¹² Lagier et al (2020) found that HCQ combined with AZM for at least 3 days decreased the need for Intensive Care Unit (ICU) among 3737 COVID-19 patients in Marseille, France.¹¹³ Arshad et al (2020) also showed that among 2541 patients treated with HCQ alone, AZM alone, and HCQ plus AZM, treatment with HCQ or HCQ plus AZM was associated with lower mortality.¹¹⁴ Another study from China indicated that treatment with HCQ alone reduced the incidence of pneumonia among 62 patients with mild COVID-19 in a randomized clinical trial.¹¹⁵ Million et al (2020) also found that the combination of HCQ with AZM reduced mortality in patients with uncomplicated COVID-19.¹¹⁶ Gautret et al (2020) also showed that AZM combined with HCQ significantly reduced the multiplication of the COVID-19 virus.¹¹⁷ The initial study by Gautret et al (2020) demonstrated the potential benefits of HCQ; however, as mentioned, the study was severely criticized as no control arm was involved.^{30,39,40}

Overall, though, HCQ was found not to effectively prevent or treat mild, moderate, or severe COVID-19 infections in prospective randomized clinical trials and retrospective and observational studies. This, together with safety concerns, prompted the WHO to drop HCQ from the solidarity trial.⁴⁴ The National Institute of Health in the USA also dropped HCQ from its studies because HCQ could not slow disease progression, pneumonia, acute respiratory distress, and death.¹¹⁸

Lopinavir (LPV)/Ritonavir (r)

Lopinavir/ritonavir blocks an enzyme known as 3CLpro, a major CoV protease enzyme that cleaves the

polyproteins during viral replication by arresting COVID-19 multiplication and spread. Consequently, an LPV/r combination may be useful in treating mild, moderate, and severe COVID-19 infection.¹¹⁹ In a triple therapy study, LPV/r was potentially promising by suppressing the viral load, while methylprednisolone reduced the incidence of pneumonia and the need for ICU admission.¹²⁰ Ye et al (2020), in an early study in China involving 47 patients, revealed that lopinavir/ritonavir lowered body temperature and restored normal physiological functions more effectively than seen in a control group.¹²¹ A retrospective observational study was undertaken in Nigeria by Bowale et al (2020), who reported the benefit of LPV/r as it significantly reduced hospital stay duration.¹²² However, in an open-label, randomized controlled clinical trial, LPV/r produced no clinical evidence of efficacy among 199 COVID-19 patients.¹²³ Li et al (2020), in their randomized controlled study in China involving 86 patients, also found no clinical benefit from LPV/r versus umifenovir among patients with mild to moderate COVID-19.¹²⁴ Also, the UK recovery study randomizing 1596 patients to LPV/r versus 3376 patients receiving usual care showed no benefit from LPV/r.⁵¹ Interestingly, recent studies revealed that the addition of another drug like methylprednisolone or umifenovir to LPV/r improves the treatment outcomes.^{120,125} However, another study, despite the addition of umifenovir, reported otherwise.¹²⁶ Equally, lopinavir, in addition to oseltamivir and ganciclovir, showed no efficacy in all groups of COVID-19 patients enrolled.¹²⁷ Consequently, further studies are needed before any recommendation can be made regarding LPV/r's role in managing patients with COVID-19. In the meantime, as mentioned, the WHO has suspended LPV/r from the solidarity trial.⁴⁴

Favipiravir (FPV)

The mechanism of action of favipiravir involves inhibition of RNA-dependent RNA polymerase enzyme, thereby inhibiting viral RNA synthesis.¹²⁸ Chen et al (2020) undertook a recent clinical trial involving FPV combined with umifenovir. The authors reported that umifenovir and FPV were not effective in treating patients with COVID-19 infection among 240 patients enrolled.¹²⁸ Similarly, another study indicated that FPV was not effective in reducing viral load.¹²⁹ However, two recent clinical trials revealed that FPV administered to COVID-19 patients showed a faster recovery than the control group.^{130,131} Overall, there is currently insufficient evidence to suggest

that the FPV has significant antiviral activity against COVID-19 and could be recommended as a future treatment.

Triazavirin

Triazavirin is a guanine nucleotide analog antiviral initially developed in Russia. Triazavirin acts via inhibition of RNA-dependent RNA polymerase enzyme, thereby inhibiting viral RNA synthesis.¹³² In their study, Wu et al (2020) found that patients administered triazavirin required fewer respiratory, cardiac, hepatic, or renal support therapies than the control group.¹³² However, despite the possible benefit observed, a large randomized, controlled clinical trial is needed before the place of triazavirin can be determined in COVID-19 patients.

Umefenovir

The mechanism of antiviral activity of umefenovir is via blockade of viral entry into the host's cell and therefore protects it from viral infection.¹³³ Lian et al (2020), in a retrospective observational study, reported that umifenovir was no better than the control group in suppressing the viral load when administered to 81 COVID-19 patients.¹³³ This implied that umifenovir monotherapy should not be used in the management of COVID-19 patients.

Remdesivir

Remdesivir is a monophosphoramidate adenosine analogue that targets and inhibits RNA-dependent RNA polymerase enzyme, thereby inhibiting viral RNA synthesis. Remdesivir has both in-vitro and in-vivo antiviral activity against several viruses, including SARS-CoV-2. As a result, remdesivir may have a place in patient treatment with mild to moderate COVID-19 disease.^{119,134} Conversely, the initial studies with remdesivir failed to demonstrate clinical benefit over placebo; however, there were concerns that the investigations were underpowered.^{32,135} Spinner et al (2020), in a study involving 596 COVID-19 patients, found those patients randomized to a 10-day course of remdesivir did not show a statistically significant improvement in their health status versus standard care randomized. However, those receiving a 5-day course had improved outcomes versus standard care, but the clinical impact was uncertain.³⁸ On the other hand, Grein et al (2020) among 61 patients with severe COVID-19 who took remdesivir for compassionate use showed significant improvement in the health status of 68% of those enrolled.¹³⁶ More recently, a larger-scale

study conducted among 1062 COVID-19 patients by NIH in the USA showed encouraging results, including a reduction in recovery time and a trend towards lower mortality.¹³⁷ This resulted in an emergency use and authorization by the US Food and Drug Administration and an endorsement by the European Medicines Agency and the National Health Services in the UK.^{45,138–141} Patient's liver and kidney function must be monitored during treatment to help minimize any adverse drug reactions.¹⁴² However, more recent evidence has resulted in WHO guidelines no longer recommending the use of remdesivir in hospitalized patients with COVID-19. This is based on the reports that remdesivir could not reduce mortality, the need for mechanical ventilation, or the duration of hospital stay.^{134,143} Consequently, further large-scale RCTs are needed to better understand the role of remdesivir in the management of patients with COVID-19.⁷⁸

Dexamethasone and Other Steroids

The mechanism of action of corticosteroids in the treatment of patients with COVID-19 involves inhibition of inflammatory mediators and the inflammatory process. It begins with pro-inflammatory genes that encode cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors.^{134,144} Recent WHO guidelines give a strong recommendation on the use of systemic corticosteroids in patients with severe COVID-19; however, it discourages the use of systemic corticosteroids in patients with mild-moderate COVID-19 infection.¹³⁴ This is based on the findings of the UK recovery group lead by Horby et al (2020), where dexamethasone appears to be the most promising treatment to date as it significantly reduced mortality and the duration of hospital stay among 6425 patients with severe COVID-19.³⁶ In another study involving Intensive Care Unit (ICU) patients, early administration of dexamethasone also reduced the duration of mechanical ventilation and mortality.¹⁴⁵ Methylprednisolone has also been shown to significantly decrease lung inflammation among 85 COVID-19 patients.¹⁴⁶ Ruiz-Irastorza et al (2020) in their study involving 242 patients also showed that methylprednisolone was effective in improving respiration among 242 COVID-19 patients.¹⁴⁷ Rahman et al (2020) in an observational study involving 136 COVID-19 patients admitted to ICU also found that early administration of steroids improved survival and decreased ICU stay.¹⁴⁸ In line with this, a recent meta-analysis from the WHO rapid appraisal team reported that critically ill COVID-19

patients who received systemic corticosteroids were associated with lower mortality than placebo or usual care.³⁵ Mikluska et al (2020) also reported that methylprednisolone on its own or combined with tocilizumab among 130 COVID-19 patients improve outcomes in non-intubated patients with COVID-19 pneumonia.²⁷

Tocilizumab (TCZ)

Tocilizumab is a humanized monoclonal antibody that inhibits the interleukin-6 (IL-6) receptor. It is employed in the treatment of rheumatoid arthritis and other auto-inflammatory processes. It is also useful in treating severe cytokine release syndrome (CRS) induced by the chimeric antigen receptor. Consequently, TCZ, an IL-6 receptor blocker, may be suitable in treating patients with severe pneumonia.¹⁴⁹ Toniati et al (2020) found that TCZ significantly reduced the need for mechanical ventilation and improved lung function among 100 COVID-19 patients.¹⁵⁰ Sciascia et al also found in an off-label, non-randomized, single-center study that tocilizumab relieved bronchial inflammation among 63 COVID-19 patients.¹⁵¹ A recent retrospective, observational study by Biran et al (2020) demonstrated that TCZ significantly reduced mortality among 630 COVID-19 patients requiring ICU.¹⁵² Guaradi et al (2020) also showed that TCZ effectively relieved inflammation among patients with severe COVID-19.¹⁵³ Moreno et al (2020) also found that TCZ decreased mortality and duration of hospital stay in critically ill patients but seemed to have a high risk of serious infections.¹⁵⁴ Similar outcomes were reported in another related study involving 158 COVID-19 patients.¹⁵⁵ Somers et al (2020) also found that tocilizumab significantly decreased mortality among 154 patients with severe COVID-19.¹⁵⁶ Furthermore, in research carried out by Yale University School of Medicine, tocilizumab reduced the need for mechanical ventilation and improved inflammatory biomarkers.¹⁵⁷ Other studies also reported comparable outcomes.^{158,159} Xu et al (2020) from China revealed that tocilizumab significantly improved clinical outcomes and reduced mortality among patients with severe COVID-19.²⁸ It also reduced the risk of cytokine storms among COVID-19 patients in another study.¹⁶⁰ Research undertaken by Klopfenstein et al (2020) also indicated that TCZ reduced the number of patients requiring ICU and death in patients with severe COVID-19.¹⁶¹ Similar outcomes were reported by Gupta et al 2020.¹⁶² The abilities of the TCZ to relieve inflammation and cytokine storms

among COVID-19 patients were further justified in a recent meta-analysis.¹⁶³

In contrast, Colaneri et al (2020) reported that TCZ did not reduce mortality or the number of ICU admission among 112 patients with severe COVID-19.¹⁴⁹ Knorr et al (2020), in a study conducted in the US involving 66 patients, also found limited clinical improvement with TCZ in patients with severe COVID-19 in a retrospective observational study.¹⁶⁴ Kewan et al (2020) also reported similar therapeutic failure in treating COVID-19 patients with TCZ.¹⁶⁵ Other researchers reported similar findings.^{165–170} In addition to a lack of effectiveness with TCZ, Moreno Perez et al (2020) also found that critically ill patients taking TCZ appeared to have a high risk of severe infections.¹⁵⁴ Consequently, despite the promise shown by tocilizumab in relieving inflammation, decreased mortality, and duration of hospital stay in some studies, we believe more research is needed before the place of TCZ in the treatment of patients with COVID-19 can be fully elucidated.¹⁶³

Other Treatments

Other investigational treatments for COVID-19 involve convalescent plasma (CP) from previously infected and recovered patients.¹⁷¹ Duan et al (2020), administering CP from donors with a high level of SARS-CoV-2 antibodies early in the disease, found this effective in boosting immunity among ten COVID-19 patients enrolled in the clinical trial.¹⁷² In addition, CP produced faster recovery among 49 COVID-19 patients in a retrospective observational study.¹⁷³ Related findings were obtained among twenty-five COVID-19 patients enrolled in a similar investigation.¹⁷⁴ A recent meta-analysis revealed that previous studies involving the transfusion of CP to patients with deadly Ebola, SARS-CoV-1, and H1N1 viruses improved patients' immunity, suppressed the viral load, and reduced the duration of hospital stay and mortality with minimal side effects.¹⁷⁵ Nonetheless, the Indian Council of Medical Research published an open-label phase-2 multicenter randomized controlled trial (placid trial). Their research findings revealed that CP did not decrease COVID-19 severity and mortality rate.¹⁷⁶ Consequently, further studies are needed before the use of CP in patients with COVID-19 can be fully elucidated.

Anakinra is a proinflammatory interleukin (IL)-1 α and IL-1 β inhibitor which has been used with some success to treat macrophage activation syndrome (MAS) and severe

cytokine release syndrome (CRS) caused by various inflammatory conditions.¹⁷⁷ Cavalli et al (2020) have reported that high-dose anakinra was safe and associated with clinical improvement in patients with moderate COVID-19.¹⁷⁸ However, further studies are imperative before any comments can be made regarding the effectiveness and safety of anakinra in patients with COVID-19.

Discussion

The studies reviewed indicate concerns with a number of the proposed treatments. Principally, HCQ with or without AZM appeared unable to effectively prevent or treat COVID-19 alongside potential harm despite the initial hype. The lack of efficacy of HCQ with or without AZM implies they were not capable of blocking the COVID-19 virus from binding and invading the host's cell. This suggests the possible use of multiple mechanisms of pathogenesis by the COVID-19 virus. Henceforth, an evidence-based approach is critical when authorities and governments recommend treatment modalities. This is endorsed by the subsequent findings with lopinavir/ritonavir and the more recent studies with remdesivir. Lopinavir/ritonavir and remdesivir were not effective in inhibiting COVID-19 replication within the host's cell. This signifies that the COVID-19 virus may employ multiple replication modes beyond inhibition of protease and RNA polymerase enzymes. There is more robust clinical evidence for dexamethasone and methylprednisone in symptomatic treatment. These steroids significantly reduced inflammation due to viral pneumonia, thereby decreasing mortality, the need for mechanical ventilation, and the duration of hospital stay.

However, further studies are needed to define optimal doses fully. Furthermore, promising results were obtained with TCZ to improve lung function and reduce mortality among patients with severe COVID-19. TCZ targets and inhibits interleukin-6 leading to cytokine storm prevention responsible for respiratory depression and deaths. However, again more studies are needed to assess its role and value given the contradictory findings to date. Convalescent plasma may also have a place in the treatment of mild COVID-19 when administered early. This is because of the timely administration of CP to COVID-19 patients helps develop strong immunity and eliminates the SARS-CoV-2 virus. However, further randomized clinical trials are needed involving many patients before CP can be fully integrated into conventional treatment.

Consequently, healthcare providers should observe caution in any off-label prescription until confirmatory studies are reported. Despite the earlier reviews undertaken on various treatment options for COVID-19, we further investigated the outcome of several randomized controlled clinical trials and retrospective observational studies. This objective was to build on existing knowledge and to stimulate further debate that could lead to the emergence of a more evidence-based therapeutic option.

Conclusions

COVID-19 Pandemic has affected almost every country in the world. The disease currently has killed over one million people globally and has significantly ravaged individuals, communities, national and international economies. The United Nations and countries have made several efforts to reduce prevalence and mortality rates. Many medicines, including repurposed medicines,^{179–181} have been the subject of clinical trials given the urgent need to reduce current morbidity and mortality rates. Pharmaceutical companies and reputable health institutions have also been working to produce an effective and safe vaccine. Whilst there was initial hype surrounding medicines such as HCQ, dexamethasone has shown promise in the symptomatic treatment of COVID-19 patients with severe pneumonia.

Nonetheless, to date, no single confirmed therapeutic option for patients with COVID-19 has been fully elucidated. This endorses the need for all key stakeholders to instigate evidenced-based approaches and not rush to administer unproven treatments that may result in more harm than good. We further await the reports of ongoing research, including new vaccines, with the hope of providing clinicians with more information to enable evidence-based decision-making on the treatment options for COVID-19.

Limitations of the Study

- 1) Heterogeneous cohort studies were included.
- 2) Pre-print articles were also included because research in COVID-19 infection is a novel and continuously evolving study area.
- 3) The research has no supporting fund to enable the purchase of articles that are not open access.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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