

**PHARMACOLOGICAL TREATMENTS OF COVID-19 – A REVIEW**JEEJA MATHUMMEL CHERUMANALIL<sup>1\*</sup>, JAYAKRISHNAN THAYYIL<sup>2</sup><sup>1</sup>Department of Pharmacology, Government Medical College, Idukki, Kerala, India. <sup>2</sup>Department of Community Medicine, Government Medical College, Calicut, Kerala, India. Email: jayanjeeja@yahoo.co.in

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**ABSTRACT**

Now the world stands in the fight against coronavirus disease 2019 (COVID-19), with its early origin from Wuhan city in China. It has evolved into a global pandemic resulting into a significant burden to the human race. As per WHO, on July 31, 2020, there were 170 million cases reported all over the world, with 6.73 lakhs deaths. There is no effective treatment so far discovered for the severe acute respiratory syndrome-CoV2. Many pharmacological agents/therapies are being used or considered for treatment. In many countries, physicians are giving COVID-19 patients treatment that has not been approved for this disease. They are treating patients using medications outside their indicated, approved uses and without study protocols, with little scientific evidence. At present, there is no evidence from randomized clinical trials (RCTs) that any potential therapy improves outcomes in patients with COVID-19. There are no clinical trial data supporting any prophylactic therapy. Along with Solidarity trial, many active clinical treatment trials are underway. This narrative review summarizes current evidence regarding major proposed treatments, repurposed or experimental, for COVID-19 and provides a summary of current clinical experience and treatment guidance for this pandemic novel coronavirus.

**Keywords:** Pharmacological management COVID-19, Interferon beta 1a, Tocilizumab, Remdesivir, Hydroxychloroquine, Favipiravir, LPV/r, Dexamethasone.

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**INTRODUCTION**

Now the world stands in the fight against coronavirus disease 2019 (COVID-19), with its early origin from Wuhan city in China has evolved into a global pandemic demanding a significant toll on the human race. As per WHO, on July 31, 2020, there were 170 million cases reported all over the world, with 6.73 lakhs deaths, and the USA is the worst sufferer, in terms of numbers, due to the disease [1]. Maximal precautionary measures and resources have been put forward by most nations to alleviate transmission and decrease mortality rates. Till date, there is no effective treatment so far discovered for the severe acute respiratory syndrome (SARS)-CoV2. For prevention, currently, 142 candidate vaccines are in the preclinical phase and 24 in the clinical phase, of which three entered in phase 3 stage. One indigenous vaccine has entered the phase 1 stage in India [2-6].

All over the world, many drugs and therapies are being considered or used for treatment. Doctors are using treatments that have not been approved for COVID-19. They are treating patients using drugs beyond their indicated, approved uses and with little scientific evidence or by extrapolation from *in vitro* studies revealing their antiviral and anti-inflammatory properties [7-9]. China, where the pandemic was originated, hospitals are using traditional Chinese medicine, which has been reported to be with good effects [10-13].

Since severe acute respiratory syndrome (SARS)-CoV-2, the causative agent of COVID-19 has a close genetic resemblance with the SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV, drugs used to treat SARS and MERS was utilized to explore the extent of their activity against SARS-CoV-2. With the sudden and severe nature of the disease and its high rate of contagion, and the costs and time involved in the development and marketing of a new, safe and efficacious drug, researchers around the world are looking to repurpose known drugs to treat COVID-19 [3]. A wide range of drugs that have earlier been approved for other indications, off label use as well as several investigational drugs is being studied through clinical trials for benefit. There are currently no drugs approved for pharmacological treatment and only very few have reported to be shown some hope. Due to the

urgent need for effective treatments, there has been increased interest in repurposing currently available drugs for immediate use [14]. As a large number of people all over the world are getting infected and hospitalized with SARS-CoV2 along with clinical trials generating medical information in a rapid pace, clinicians need accurate evidence regarding effective medical treatments [8]. In this context, this narrative review summarizes current evidence regarding major proposed treatments, repurposed or experimental, for COVID-19 and provides a summary of current clinical experience and treatment guidance for this.

**HYDROXYCHLOROQUINE (HCQ) AND CHLOROQUINE (REPURPOSED OR OFF-LABEL)**

Chloroquine and HCQ both belong to the same group 4-aminoquinolines. The former is an antimalarial agent with anti-inflammatory and immune-modulatory activities, has gained significant interest as a potential therapeutic option for the management of COVID-19. HCQ a less toxic derivative of chloroquine has demonstrated more potent inhibition of SARS-CoV-2 virus *in vitro* studies [15,16]. While the exact mechanisms of action are unknown, it is considered that these effects are mainly through alkalization of the phagolysosome as well as inhibition of viral entry by blocking receptor binding and membrane fusion [17-21]. It has been used widely for a long time for treating conditions such as rheumatoid arthritis (RA), juvenile idiopathic arthritis, and Sjogren's syndrome [22]. Its lesser cost, fewer side effects, and safety in pregnancy make it more preferable to chloroquine [17,18]. On prolonged treatment, it may rarely cause cardiotoxicity manifested as cardiomyopathy or conduction abnormalities [22,23].

Although there was no evidence exists for the efficacy of HCQ treatment of coronavirus such as SARS or MERS, the earliest trials conducted in China revealed that HCQ has *in vitro* activity against SARS-CoV-2 [24]. One open-label, randomized controlled trial (RCT) conducted in China using HCQ in 150 patients with mild to moderate COVID-19 shows HCQ did not result in any benefit than the standard of care alone and adverse events were higher [25]. A French study among a cohort of heterogeneous patients, it has been shown to reduce SARS-CoV-2 viral loads at day 6 compared to controls [26]. However, this study has been

criticized widely for its methodological flaws and the findings were refused [27]. In a RECOVERY trial conducted in the UK, among 1542 patients randomized to HCQ compared with 3132 patients to standard care alone, reported that there was no significant difference in the primary endpoint of 28-day mortality of 25.7% HCQ versus 23.5% and the hazard ratio was 1.11 (95% confidence interval 0.98–1.26;  $p=0.10$ ). There was also no evidence of beneficial effects on hospital stay duration or other outcomes [28]. The other two published non-randomized comparative studies suggest an increased risk of QT prolongation among patients receiving HCQ compared to those not receiving HCQ (RR: 2.89; 95% CI: 1.62, 5.16) [29]. A chloroquine trial in Brazil was stopped due to the risk of fatal heart complications like arrhythmia [30].

Some countries, including India HCQ, have been suggested for prophylaxis among healthcare workers who are taking care of COVID-19 patients and household contacts of patients without any evidences. Experts have warned that, if any, the potential benefit must be weighed against their increased risk of life-threatening arrhythmias. In June 2020, the first-ever internationally reported RCT conducted ( $n=821$ ) to study the prophylactic efficacy of HCQ for preventing COVID-19 reported that the incidence of illness did not differ significantly between participants receiving HCQ (11.8%) and those receiving placebo (14.3%) [31]. As per the Infectious Diseases Society of America (IDSA) report on June 22, the currently available best evidence failed to demonstrate or to exclude a beneficial effect of HCQ on clinical progression of COVID-19 as inferred by radiological findings; (risk ratio – RR: 0.61; 95% CI: 0.26, 1.43) or on viral clearance by PCR tests (RR: 2.00; 95% CI: 0.02, 20.00) [29].

Antibiotic azithromycin (AZT), used for the respiratory tract, skin infections have been used in the treatment of some viral respiratory tract infections like influenza as an adjunctive. Along with antibacterial coverage, it has got some immune-modulatory and anti-inflammatory effects [32,33]. Recently, it has been proven to be *in vitro* active against Zika and Ebola viruses [34-36].

With the above assumptions, some investigators have added AZT along with HCQ in suspected bacterial infections in COVID-19. An observational study with AZT conducted on 11 hospitalized patients remains positive for COVID-19 even after 5–6 days of the treatment [35]. In another retrospective multicentric four-arm comparative study at New York among 1438 hospitalized patients, the mortality rate was found to be more with HCQ plus AZT and also the cardiac arrest was significantly higher with the combination therapy, compared to either drug alone [37]. In a large cohort study, patients taking a 5-day course of AZT had an increased risk of sudden cardiac death with an HR of 2.71 (95% CI 1.58–4.64) versus 0.85 (0.45–1.60), compared to patients receiving no antibiotic or amoxicillin, respectively [38]. Hence, it is better to avoid this combination therapy in a vulnerable population.

WHO in its technical guideline states that there is not, as yet, definitive pre-clinical or clinical evidence demonstrating the efficacy of HCQ as a prophylactic agent for COVID-19 [39]. On June 17, 2020, WHO announced that the HCQ arm of the Solidarity trial was being stopped because data from the trial showed that among hospitalized COVID-19 patients compared to those with on standard care, the mortality was not reduced by HCQ. WHO also mentions that this decision applies only to the conduct of the Solidarity trial and does not apply to the use or evaluation of HCQ in pre/post-exposure prophylaxis in patients exposed to COVID-19.

The dosage recommendation for HCQ has also varied widely: The prophylactic regimen recommended by Indian Council of Medical Research (ICMR) advised that 400 mg of HCQ be given twice on day 1, then 400 mg once weekly for 7 weeks for healthcare workers or 3 weeks for asymptomatic contacts [40]. Chinese experts recommended dosage of HCQ at 500 mg twice daily for 10 days [41]. Earlier with the non-availability of any approved available drug US FDA has

approved HCQ to treat COVID-19 on an emergency basis. The approved therapeutic dose for HCQ was 800 mg on day 1, followed by 400 mg daily for 4–7 days [42]. As such, the evidence base behind the use of HCQ as prophylactic or therapeutic remains limited as with other drugs and should only be used after shared decision making with the patients while awaiting the results of other on-going studies.

#### REMDESIVIR (RDV)

RDV is a prodrug of a nucleotide analog and RNA polymerase inhibitor and a novel broad-spectrum antiviral agent originally synthesized and developed in 2013–2014 to treat infections by hepatitis C virus and respiratory syncytial virus by Gilead Sciences [43]. During the 2014 Ebola virus outbreak, RDV demonstrated activity against Ebola virus in cell lines and in Rhesus monkeys infected with the virus [44,45]. However, clinical efficacy was not conclusively demonstrated in the treatment of Ebola or Marburg infections [38,46]. By *in vitro* and animal studies, it has documented activity against SARS-CoV and MERS [47,48]. Since it is a new drug, the clinical safety data were not adequately demonstrated. The documented adverse effects are gastrointestinal symptoms, elevated transaminases, and longer clotting times, and possible drug interactions with co-administration of other drugs like CYP enzymes inducers [49]. Like HCQ, many clinical trials are being conducted to explore the efficacy and safety of RDV in COVID-19 [24,47,50,51]. The dosage advised for RDV for a 10-day regime was: 200 mg loading dose on day one, followed by 100 mg once-daily maintenance doses for 9 days, which was similar to that of the clinical trial against the Ebola virus [52,53].

In a cohort study funded by Gilead Sciences, where RDV was administered on a compassionate basis on April 2020, clinical improvement was observed in 36/53 (67.9%) patients [54]. This paper also reported that RDV administration for 10 days was associated with adverse events in 32/53 (60.3%) patients, of which 23% were serious and four patients discontinued RDV treatment prematurely [54]. Another study conducted in China, 237 patients admitted to hospital with severe diseases 158 to RDV and 79 to placebo, found that there was no difference in time to clinical improvement with the use of RDV with a hazard ratio 1.23 (95% CI 0.87–1.75). The adverse events were reported among 66% of RDV recipients versus 64% placebo recipients. RDV was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients with placebo and was not associated with statistically significant clinical benefits [55]. Moreover, RDV was not associated with significant mortality benefit after 28 days of hospitalization, and virological clearance was observed in only 37/236 (19%) patients. Since there were no significant clinical benefits, this trial was terminated prematurely. The explanation given by the authors for termination was that the pandemic had been brought under control in China and it was difficult for recruiting new COVID-19 cases for the study that has received many criticisms [55]. On May 1, 2020, the US FDA granted an Emergency Use Authorization (EUA) for RDV to treat patients with “suspected or laboratory confirmed” severe COVID-19, based on a review of top-line data from two trials at US (NCT04280705, NCT04292899) [56]. The first study was sponsored by the National Institute of Allergy and Infectious Diseases and the preliminary data of the study reported that compared to placebo, RDV shortens time to recovery from 15 days to 11 days (31%) significantly without any significant mortality benefit [57]. Another study reported patients ( $n=1059$ . 538 vs. 521) receiving treatment with RDV had a shorter median time to recovery (median 11 vs. 15 days; HR: 1.32; 95% CI: 1.12, 1.55; high certainty of evidence). The Kaplan–Meier estimates of mortality by 14 days were 7.1% with RDV and 11.9% with placebo (HR: 0.70; 95% CI: 0.47–1.04) [58]. IDSA opined that additional clinical trials are needed to provide increased certainty about the potential for both benefits and harms of treatment with RDV, as well as understand the benefit of treatment based on disease severity [29]. Meanwhile, after EUA was granted for RDV use to treat COVID-19 patients in the USA, to enhance drug supply to countries, manufacture of RDV was started in India as on May 12, 2020. The Institute for Clinical and Economic Review estimated that for a 10-day course of RDV, the production cost

will be only USD 10, but they are having a retail price of USD 4500 [59]. On June 1, 2020, Drug Controller General of India (DCGI) has granted restricted emergency use of RDV in hospitalized COVID-19 patients with moderate disease (those on oxygen) with few of contraindications like severe renal impairment, pregnancy or lactation and children below 12 years of age. Dose: 200 mg IV on day 1 followed by 100 mg IV daily for 5 days [59]. For final approval of RDV for treating COVID-19, also need further evidence proofs.

#### FAVIRAVIR

Favipiravir is an oral antiviral drug discovered, approved, and manufactured by Toyama chemical in Japan. It is a purine nucleic acid analog and potent RNA dependent RNA polymerase (RdRp) inhibitor [60]. In the human body, enzymes will convert to its active metabolite (ribofuranosyltriphosphate) which inhibits RdRp which are necessary for the transcription and replication of viral genomes. It is well absorbed after oral administration and its bioavailability is almost complete, but food will interfere with absorption. The drug undergoes hydroxylation primarily by aldehyde oxidase and to a lesser extent by xanthine oxidase to its inactive metabolite and T<sub>1/2</sub> is about 2–5.5 h, which is eliminated mainly through the renal route [61–63]. The drug has got adverse effects on hematopoietic tissues and liver, resulting in reduced RBC production, increase in liver enzymes, rise in total bilirubin, and vacuolization in hepatocytes. It has got teratogenicity effects [61,62]. With the limitations of the scientific evidence and doubted safety concerns, widespread use of favipiravir against COVID-19 is warranted.

The drug was initially approved for therapeutic use in resistant cases of influenza and later has been investigated for the treatment of diseases such as Ebola, Lazza, and now COVID-19. *In vitro*, it has proved activity against other RNA viruses and the EC<sub>50</sub> of favipiravir against SARS-CoV-2 was 61.88 µM/L in Vero E6 cells [24,64]. However, limited clinical experience has been reported for supporting the use of favipiravir for COVID-19. It is currently being tested in 18 clinical trials for COVID-19 and results from two studies have shown a positive outcome, while data from other trials are waiting [65]. An RCT conducted in China (ChiCTR 200030254) among 120 each COVID-19 patients have shown that favipiravir has a good recovery rate (71.43%) compared to umifenovir (55.86%) p=0.001, and the duration of symptoms such as fever and cough significantly shorter, with more ADR [65]. Another RCT (<https://clinicaltrials.gov/ct2/show/NCT04359615>) was going on in Tehran, Islamic Republic of Iran and a phase II trial among 50 patients are going on at the University of Massachusetts Medical School, US. In a trial among 2000 patients, it has demonstrated safety and clearance of the influenza virus by 6–14 h [65]. Glen mark, the manufacturers of favipiravir, claimed that the drug shows a clinical improvement of up to 88% in COVID-19 with a rapid reduction in viral load by 4 days. In India, a randomized multicentric study was done among 150 patients to test the drug's efficacy and safety; the study details are yet to be published [66]. Based on the data, they obtained approval for manufacture and marketing the drug for emergency restricted use for the treatment of mild to moderate patients. The DCGI without publicizing the basis of a clinical trial conducted in India has given accelerated approval to Glen mark Pharmaceuticals, an Indian pharmaceutical company on an emergency basis, to sell generic versions of favipiravir for the treatment of COVID-19 [67]. Although there is no scientific consensus on the efficacy of the drug, doctors in China and Russia started using it to treat COVID-19 patients. The drug was not yet approved by the US and UK [65]. The authors are unable to find well-designed scientific studies supporting the effectiveness and safety of this drug in COVID-19 patients. Therefore, the explanation that the grant was approved based on "evaluation of data" does not seem tenable [66].

#### TOCILIZUMAB (TCZ) (OFF LABEL)

TCZ is an immunosuppressive drug, mainly for the treatment of RA and systemic juvenile idiopathic arthritis, developed by Roche and Chugai Pharmaceutical [68]. It is a humanized monoclonal antibody

against the interleukin-6 (IL-6) receptor by blocking their receptor. IL-6 is a cytokine that plays an important role in immune response and is implicated in the pathogenesis of many diseases such as autoimmune diseases, multiple myeloma, and prostate cancer. The drug is emerged as an alternative treatment for COVID-19 patients with a risk of cytokine storms. Safety in pregnancy and harm to the fetus was unknown [69]. They suggested that in patients with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not improving despite the use of steroids, TCZ may be considered. Dose prescribed is: 8 mg/kg (m. maximum 800 mg at one time) given slowly in 100 ml normal saline over 1 h; dose can be repeated once after 12–24 h if needed [69,70]. Among COVID-19 patients, the long-term safety data of TCZ were still unknown.

In a retrospective study conducted in China on 15 subjects out of the four critically ill patients, three died, and one patient did not show a decline in C reactive protein levels. Ten patients achieved clinical stabilization and disease progression was seen in two cases [71]. Another study conducted by Xu *et al.* indicates the potential benefits of TCZ in lowering mortality in severe COVID-19 patients [69]. A prospective study among 63 patients shows administration of TCZ on 1<sup>st</sup> day of hospital admission increases the survival chances of severe COVID-19 patients [72]. An Italian study conducted among 100 patients reported a rapid, sustained, and significant clinical improvement [73]. A retrospective cohort study conducted in Italy among 544 severe COVID-19 pneumonia, compared with the standard care group 73 (20%), the death rate among the TCZ group was low 13 (7%; p<0.0001). After adjustment for sex, age, recruiting center, duration of symptoms, and SOFA score, TCZ treatment was associated with reduced risk of invasive mechanical ventilation or death (Hazard ratio 0.61, 95% CI 0.40–0.92), thus reported to reduce the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia [74]. In a controlled observational study among 154 mechanically ventilated patients with severe COVID-19, TCZ was associated with a 45% reduction of death, despite a very high frequency of superinfection (54% vs. 26%) [75]. On the harm side, other non-COVID patients receiving TCZ were reported to be prone for other severe infections, allergic reactions [29]. Since the results of RCTs were not yet available, IDSA guideline panel recommends TCZ only in the context of a clinical trial. (Knowledge gap) [29]. Although unproved, it was recommended in India by ICMR for emergency use. After analyzing the results of RCT-COVACTA trial on July 29, 2020, TCZ, Roche's Head of global product development, publicize that TCZ fails to address COVID-19 pneumonia [76].

#### CORTICOSTEROIDS: DEXAMETHASONE

Corticosteroids consist of natural glucocorticoids, mineralocorticoids, and their synthetic analogs. They have an anti-inflammatory response as well as immunosuppressant actions. As a potent anti-inflammatory and anti-fibrotic drug, it may have actions to prevent an extended cytokine response and may speed up the resolution of pulmonary and systemic inflammation in COVID-19 pneumonia [77,78]. At the same time, there is concern that the use of corticosteroids may have negative effects by inhibition of immune response and pathogen clearance in COVID-19 [77]. At the onset of the pandemic, due to lack of evidence from clinical trials, WHO advised against the use of steroids in COVID-19 patients. However, a low dose systemic corticosteroid was indicated by Society of Critical Care Medicine and European Society of Intensive Care Medicine for treating mechanically ventilated COVID-19 patients with the acute respiratory syndrome (ARDS) [79].

Dexamethasone is a glucocorticoid 5 times more potent than methyl prednisolone with profound anti-inflammatory properties and immunosuppressant action. Furthermore, it has got less mineralocorticoid activity resulting in fluid retention which can be good for ARDS patients [80]. In COVID-19 patients, it depresses the body's immune response when it becomes too aggressive to control by other means [80]. In non-COVID ARDS patients, by decreasing ventilator days and reducing mortality, the utility of dexamethasone was well proved [81].



pandemic reality, so it may not be able to give conclusions before the end of the pandemic [100].

## CONCLUSION

Thus far, in the COVID-19 pandemic, most often therapeutic management has been initiated and altered either on the basis of individual case reports and physician opinion, rather than of randomized trials. As per the above review information available till date, no new NCE/drugs were invented for COVID-19. Most of the drugs suggested were off label use. At present, there is no evidence from RCTs that any suggested therapy supporting prophylactic or curative for COVID-19. The only drug proved to be useful by large RCT was dexamethasone. Other antivirals were ruled out for its efficacy in treating COVID-19. In these uncertain situations, ideally, physicians should judiciously use drugs based on scientific evidences. So until enough evidence is gathered that one treatment is superior to another, we should be sceptical of any purported therapeutic regime and should be updated.

## AUTHORS' CONTRIBUTIONS

Both authors have contributed equally in all processes of preparing this paper (conceiving ideas, acquiring data, preparation of manuscript, reviewing, and editing manuscript).

## CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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