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The Rationale for Current Pharmacotherapy of Covid-19

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ABSTRACT

Severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS) and SARS-CoV-2 are related to the coronaviridae family. The worldwide pandemic of the new coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) broke out in Wuhan province of China, in December 2019, and spread rapidly throughout the world. More than 6 million cases and 370,000 deaths had been reported by 31 May 2020 in more than 200 countries. No data are available from any clinical trials supporting a proposed prophylactic therapy. More than 300 active clinical trials are currently underway. Many drugs have been studied against COVID-19, but there is no actual evidence from any randomized clinical trials with a potential therapy that can improve outcomes of a patient diagnosed with COVID-19. In some cases, many of the investigated drugs cause side effects, e.g. chloroquine, ribavirin. Besides its beneficial effects such as reducing disease progression and decreasing symptom duration, chloroquine can cause cardiac side effects. Ribavirin, on the other hand, is recognized as a teratogen and considered unsafe in pregnancy. No special effective antiviral therapy against COVID-19 is currently available. Although the course of the disease is mild and moderate in the majority of the COVID-19 patients, more than 5%-7% of the patients' life being under severely susceptible threats requires more effective medicinal products, urgently.

Key Words: COVID-19, Pharmacotherapy, Antivirals, Hydroxychloroquine, Supporting agents

Introduction

Severe acute respiratory syndrome (SARS-CoV), and Middle East respiratory syndrome (MERS) with SARS CoV 2 (SARS-CoV-2) relate to the coronaviridae family (1, 2). All three viruses are pathogenic and cause pneumonia in humans (3, 4). Coronavirus disease (COVID-19) was described as an epidemic by the WHO on 11 March 2020 (5). The worldwide pandemic of new coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was triggered Wuhan, China, in December 2019 and stretched rapidly throughout the world (6). More than 6 million cases and 370,000 deaths in more than 200 countries were reported by 31 May 2020. Approximately every hour a new data concerning clinical characteristics, treatment options, and consequences for COVID-19 rises up, in various stages of assessment for COVID-19. So many medications have been studied but there is actually no evidence from randomized clinical trials (RCTs) that any potential therapy improves patient outcomes with either assumed or verified by COVID-19. No data from a clinical trial supporting any prophylactic therapy are available. More than 300 active clinical trials of treatment are in progress (7). This article review sums up current evidence on major proposed treatments, re-established, for COVID-19, and includes the summary of current clinical experience and treatment advice for this novel Coronavirus pandemic. A large number of therapies such as chloroquine, hydroxychloroquine, ribavirin, lopinavir/ritonavir, favipiravir, and remdesivir (Table 1). The aim was to determine which was effective against Ebola with so many therapeutic interventions given to the affected patient (7, 8, 9). Clinical symptoms as displayed in Figure 1, the clinical spectrum of SARS-CoV-2 infection seems to be uncertain, including asymptomatic infection, moderate-higher respiratory tract disease, and critical viral pneumonitis with respiratory defect and even mortality.

Therapies for covid-19

The large majority of COVID-19 patients are cured without any medications, so there is no

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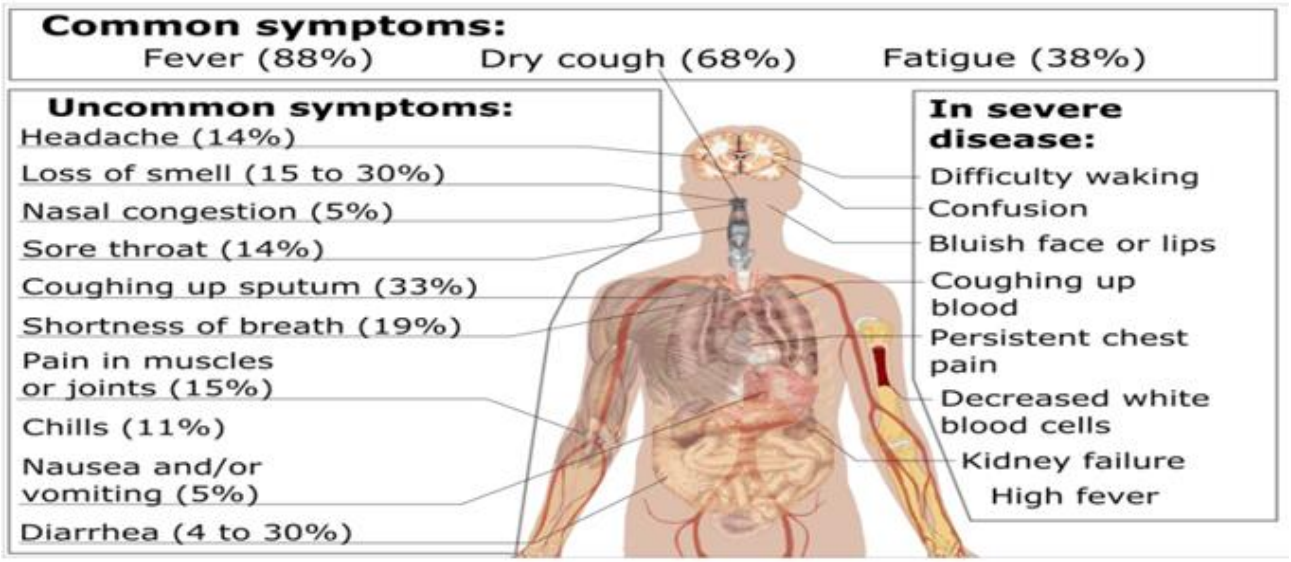

Fig. 1. Common coronavirus disease symptoms (may appear 2-14 days after exposure) (76)

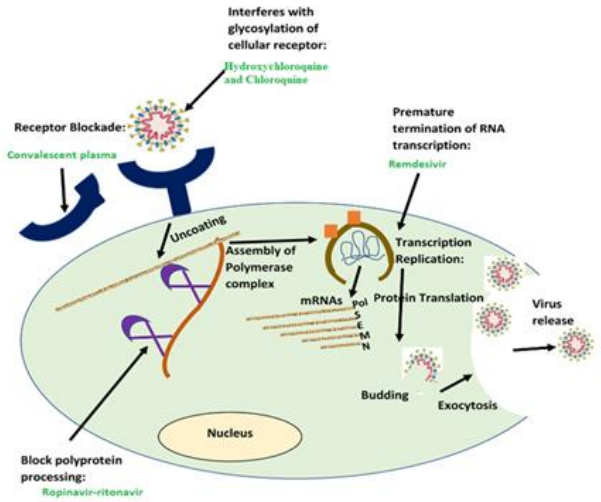

Fig. 2. Experimental therapeutic approaches attempt to interfere with various actions in the SARS-CoV-2 replication period (76)

need for antiviral therapy in most cases. However, it could lead us miss an early therapy chain, whereby the disorder becomes more modifiable, if we wait until patients are seriously ill before starting therapy. Antiviral therapy is known to offer the most advantage when started earlier during the course of the disease both in influenza and SARS (10). There are no guidelines for combinations of over 3 antivirals current care choices are focused largely on the prior experience they have clinical benefits in Influenza, Ebola, MERS and SARS treatment among other diseases of the viruses (Figure 2, 11, 76). Treatment should be given according to the nature of the condition. Indicative therapy would be used during the first phase paracetamol and potentially vitamin D is included fifty thousand units a week and four thousand every day (12).

Hydroxychloroquine and Chloroquine: Both chloroquine (CQ) and hydroxychloroquine (HCQ) are aminoquinolines, for over 50 years both of them are used for treating and autoimmune diseases in addition to their antimalarial effects, that activate of them use for autoimmune treatment, for example lupus erythematosus and rheumatoid arthritis. These two drugs could inhibit some cellular functions and molecular pathways taking part in immune stimulation. Expression of MHC class II inhibition, presentation of antigens and immune activation (reduction) CD154 expression by T cells (22). "In a study carried out in 2005" has shown that chloroquine is successful in reducing the spread of the virus to other hosts by increasing endosomal pH and thus inhibiting pH dependent steps in the viral replication cycle (23). Chloroquine, which has shown immune control by suppressing IL-6 tumor necrosis factor, can also help to avoid cytokine storm leading to dramatic reductions in COVID-19 patients (24). In addition, in a trial of more than 100 patients in China, chloroquine was shown to be very successful in treating COVID-19 pneumonia. More studies have shown that hydroxychloroquine has improved potency and a greater tolerability than chloroquine (25). Furthermore; studies have shown that these drugs interfere with ACE 2 receptor glycosylation that inhibits the SARS-CoV-2 receptor. HCQ and CQ with effective SARS-CoV-2 reported recently in vitro studies with wide array of infection (MOI) of 0.01 with an efficacy of 50 percent the use of HCQ or CQ is part of COVID-19 treatment protocols worldwide, but there are very frightening evidence to support this. An early China report suggests that use of chloroquine is

linked to reduced disease progression and decreased symptom duration (26).

Lopinavir/Ritonavir: US Food and Drug Administration (FDA) identified the combination of lopinavir and ritonavir as protease inhibitors for HIV-1 treatment. Protease enzyme is an aspartic protease which cleaves proteins from precursors (27). This refers to both functional and structural proteins. The proteases play a crucial role in the viral life cycle if they are inhibited and immature, nonpathogenic virions are formed. The microsomal enzymes "CYP3A4" and "CYP3A5" are used for extensive metabolism in the liver of lopinavir. Ritonavir inhibits the CYP3A4 enzyme (28). When the two drugs are co-administered, lopinavir becomes more common. There have been limited available studies in a systemic review of lopinavir/ritonavir for treating SARS and MERS early reports for the COVID-19 diagnosis are primarily case reports and small retrospective, nonrandomized observational studies that make it difficult to decide whether lopinavir/ritonavir is being treated directly (29). In the treatment of SARS-CoV-2, the combination has recently been tried. By comparison, the treatment with lopinavir/ritonavir was not beneficial as compared to traditional medical care in a study which included 199 patients admitted to hospital with serious COVID-19 in terms of the period for the clinical improvement, viral load or mortality (30). While more RCTs are in progress for lopinavir/ritonavir, the current data suggest a minor role in lopinavir/ritonavir Treatment with COVID-19. Lopinavir/ritonavir dosing, the most commonly used and examined. The treatment schedule for COVID-19 is 400mg/100 mg for twice a day for up to fourteen days (31).

Ribavirin: The ribavirin is a monophosphate inhibitor of inosine dehydrogenase. The enzyme is essential for guanosine de novo synthesis. The medicine is mostly used to treat hepatitis C virus. The effect as monotherapy for SARS-CoV or MERS-CoV therapy has not been significant (32). In combination with lopinavir/ritonavir and interferon-α (1a or 1b), ribavirin was also used in MERS-CoV as a cure and showed no important impact (33, 34). A systematic examination of ribavirin clinical experience inconclusive findings in 26 of the 30 SARS treatments were revealed. Reviewed studies with 4 studies showing potential harm due to negative impacts including liver and hematologic toxicity (35). Haematological toxicity is serious by the dose of ribavirin. The massive doses of haemolytic anaemia in the SARS trials were resulted. Similar safety problems have been found with approximately 40% of the highest MERS clinical trial patients with ribavirin plus blood interferon transference. 75% of SARS patients suffering from transaminase uptakes of ribavirin. Ribavirin is also a recognized teratogen and is considered unsafe in pregnancy (36).

Supporting Agents

Favipiravir: Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is an antiviral agent which inhibits RNA polymerase (RdRp) viruses selectively and potent (37). Favipiravir is approved in a number of Asian countries to treat influenza viruses of type A and B (38). In mild cases of COVID-19. Favipiravir was reported to be used with one study, in conjunction with the combined lopinavir/ritonavir, to achieve better clarification of the viruses and to improve radiology more often. Different dosing schemes based on the form were proposed infectious content. The lower dose shifts are definitely favipiravir EC50 values compared to influenza mentioned SARS-CoV-2 and Ebola. In the treatment of COVID-19 doses at the top of the dosing range must be considered. The dose of loading (2400 mg to 3000 mg every 12 hours, every two doses) is prescribed, followed by the regular dose (1200 mg to 1800 mg every 12 hours). It takes about 5 hours to live halfway (39,40,41). Favipiravir (n= 120) was compared with Arbidol (n=120) in a prospective, randomized, multicenter study for the treatment of moderate and severely infected COVID-19. Clinical recovery variations on day 7 have been noted in moderately infected patients (71.4% favipiravir and 55.9% arbidol), p = .019) (42).

Remdesivir: Is an active C adenosine nucleoside triphosphate analog pro-drug monophosphate that is subjected to an active metabolism. The agent has been detected in the course of a screening process for RNA virus antimicrobials. Coronaviridae and flaviviridae, for example. Research and creation at the Ebola height the agent showed promised virus outbreak due to low EC50 and selectiveness of host polymerase against the strain of Ebola (43). The medicine inhibits the main effects of the post-entry stage RNA-dependent RNA (RdRP) main enzyme, remdesivir also has operation In vitro research against to SARS-CoV-2 with a 1.76 μM EC50 value Vero E6 cells showing that their working degree is possibly in nonhuman mammal models to be done (44). The first patient with COVID-19 was noted in United States remdesivir was issued without apparent. Adverse effects the substantial clinical effects of oral and intravenous oselthamivir were

improved treatment of patients with influenza (45). The health and pharmacokinetics of remediation have been assessed clinical trials of single and multi-dose phase 1.63 intravenous trials 3 mg to 225 mg infusion with good evidence untolerated toxicity of liver and kidney. The current dosage under review a single charge dose of 200 mg and a daily infusion of 100 mg is needed. There should be no liver or kidney change in patients with an estimated time, but initiation is not recommended. Filtration rate of glomerular fluid below 30 mL/min (46). On 1 May 2020, the United States recently Food and Drug Administration issued authorization for the emergency use of remdesivir in COVID-19 patients. Nausea, vomiting, and liver creatine kinase elevations are negative effects of remdesivir. The use of cyclodextrin means that patients with renal disease have a risk of possible toxical accumulations of this substance. Remdesivir can only be used as an empathetic drug for children and pregnant women (47).

Azithromycin: There was no evidence that hydroxychloroquine plus azithromycin has been strongly antiviral or clinical benefits to a limited future sample. Clinical Outcomes were absorved in 11 consecutive patients who were receiving azithromycin (500 mg on the first day then 250 mg on the second day) and hydroxychloroquine (600 mg/day ten days). The study group comprised 7 men and 4 women with an average age with 58.7 years (range, 20-77 years). 8 of them were significantly affected by bad results (48). Latest studies have examined the side effects of azithromycin and hydroxychloroquine combination. A review of medical data from 956,374 patients showed a substantial increase in cardiovascular, chest pain and heart failure risk when they are treated with azithromycin and hydroxychloroquine, relative to hydroxychloroquine alone. Such results are not unique to the nature of COVID-19 infection, but show that the combination of hydroxychloroquine and azithromycin adverse cardiovascular events is much more possible (49). But one study showed that after 6 days treatment of COVID-19 patients with combination of hydroxychloroquine and azithromycin 100% of patients were virologicaly cured comparing with 57.1% in patients treated with hydroxychloroquine only (50)

Tocilizumab: The humanized monoclonal antibody tocilizumab. Which was licensed for patient treatment with arthritis rheumatoid. It is preventing the binding of IL-6 and it is substantially monocytes and macrophages increases cytokine expression in patients tempest (51). Tocilizumab was released by China National Health Commission on 4 March 2020 in the 7th Chinese Medical Guideline for Diagnosis and Treatment of Pneumonic COVID-19 Substantial lung infections and higher IL-6 rates as a choice for patients with serious COVID- 19 (52). It was accompanied by optimistic findings in the use of tocilizumab in 21 serious COWID-19 patients in China to reduce serious lung inflammation (53). Nonetheless, Health Canada confirmed that serious cases of liver injuries caused by drugs have been reported in tocilizumab-treated patients, like acute hepatic insufficiency needing a transplant (54). The appearance of symptoms must be closely monitored by patients symptoms of infection, include potential development of tuberculosis in latent tuberculosis infection tested patients before beginning care, during and after treatment with tocilizumab (55). After tocilizumab therapy, major changes in the lymphocyte percentage and CRP were observed. The percentage of lymphocytes in 10 patients returned to normal. CRP decreased significantly and returned to normal after treatment on the fifth day (56).

Umifenovir: Umifenovir/arbidol is a stronger version antiviral agent with such a lever action system interaction between the S protein/ACE2 and the cellular membrane inhibitors surrounding virus (57). Umifenovir is licensed only in a few countries including Russia and China for the prophylaxis and therapy of Type A and Type B infection and after influenza complications (58). 200 mg every 8 h by mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules for treatment of COVID-19 (59). In general, umifenovir displays a large variety of hepatitis B antiviral viruses, syncytial virus, atenovirus, arthropod-borne flavivirus including Zika virus, West Nile virus and, parainfluenza virus, avian coronavirus, coxsackie B3, hantavirus and tick-borne encephalitis (60).

Anticoagulation: The role of the hypercoagulable state leading to micro and macrovascular thrombosis in COVID-19 has been given considerable attention. In a longitudinal study of COVID-19 patients, disseminated intravascular coagulation and high d-dimer level were reported as predictors of poorer outcomes (61). Anticoagulants have reduced mortality in patients (62). Heparin is anti-inflammatory. and may also inhibit the SARS-CoV-2 Surface Receptor (Spiken) S1 viral attachment through

Table 1. Recommended pharmacological therapies for COVID-19 infection

Agent	Mechanism of action	Adult dose/administration	Current recommendations
Chloroquine phosphate (13,14)	Enhances and inhibits endosomal pH related steps in the process of viral replication.	Chloroquine as Chloroquine phosphate 500 mg by mouth every 12-24 h × 5-10 d. Available as: 250-mg tablets (salt); 500-mg tablets (salt); 500-mg tablets of chloroquine phosphate (salt) = 300-mg chloroquine base. Dose adjustments: Kidney: creatinine clearance <10 mL/min administer 50% of dose. Hepatic: No dose adjustments in hepatic impairment recommended; use with caution. Administration: Preferable to avoid crushing. If needed, may be crushed and mixed with jam, pasteurized yogurt or similar foods.	Chloroquine can be used when Hydroxychloroquine isn't available
Hydroxychloroquine sulfate (13,15,16)	Improves and prevents endosomal pH linked steps in the process of viral replication.	400 mg by mouth every 12 h × 1 d, then 200 mg by mouth every 12 h × 4 d; alternative dosing: 400 mg by mouth daily × 5 d or 200mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water or compounded into an oral solution.	Combination of Hydroxychloroquine with azithromycin suggested for patients with moderate to severe disease
Lopinavir /ritonavir (13,17,18)	Protease inhibitors that prevent the output of active viral peptides.	400 mg/100 mg by mouth every 12 h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-mg/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution, take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes.	Not recommended at this time
Ribavirin (13)	Guanosine analog that interferes with viral replication.	Not potent enough to be effective at safe doses; hematologic toxicity precludes use.	Not recommended at this time
Favipiravir (7,19)	Inhibitor of RNA polymerase.	Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available, Hepatic: Dose adjustment considered in Child-Pugh C, increased exposures observed in Child-Pugh class A to C.Administration: Tablet can be crushed or mixed with liquid, bioavailability >95%.	Not recommended at this time
Remdesivir (20,21)	Analog nucleotide used in the Chain of viral RNA and premature chain output finishing.	200 mg × 1, 100 mg every 24 h IV infusion. Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR <30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion.	Recommended for patients with severe disease and Respiratory failure

conformational changes (63). Low molecular heparin was associated with lower IL-6 serum levels in patients hospitalized by COVID-19, suggests that an additional mechanism may exist. In addition to thrombosis prevention/treatment (64).

Corticosteroids: Low doses of methylprednisolone could be used as effective anti-fibrotic anti-inflammatory and likely to prevent a prolonged cytokine reaction and can accelerate lung and systemic solution to the problem pneumonia infection (65). Some medical studies have extensively believed corticosteroids; in particular methylprednisolone can improve aberrant immune response caused by asepticism (probable side effect of COVID-19 infection) and blood pressure increases when it is low (66). Typically, 40-80 mg IV per day for 3-6 days was the most common mehylprednisolone regimens applied in China. One research showed no mortality effects and reduced viral clearance using corticosteroids. In the WHO guidelines, a corresponding study found no mortality impact (67, 68, 69).

Miscellaneous Agents and Therapies

Angiotensin-Converting Enzyme 2 Receptor: Receptor of angiotensin transfer enzyme 2 (ACE2) considered to be an important pathogenesis target COVID-19. Studies show that comorbidities have often been observed, like elevated blood pressure and diabetes in infected patients with SARS-CoV-2 when they are under treatment with inhibitors angiotensin conversion enzyme (ACE) or angiotensin blocking receptor (ARB) (70, 71, 72). However, SAR viral RNA, decreases the activity of ACE2, thereby increasing the angiotensin 2 levels after entry into respiratory epithelial cells. This could lead to serious damage to the lung (73, 74). ACEi and ARB are two associated therapy classifications widely utilized for the treatment of high blood pressure and other cardiovascular diseases. Enhancing ACE2 production on the surface of the pulmonary cell (75, 76, 77).

The COVID 19 is the world's biggest public health epidemic crisis of this generation, scientists have made progress on the new coronavirus characterisation and treatments and vaccines frequently work opposed to the virus. Approximately every hour a new data concerning clinical characteristics, treatment options, and consequences for COVID-19 rises up. So many medications have been studied but there is actually no evidence from randomized clinical trials that any potential therapy improves patient outcomes.

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