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Review Article

Clinical evaluation of selected Pharmacological Treatments used for Coronavirus (COVID-19) pandemic

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Abstract:

Background: Coronavirus is an enveloped RNA virus, from the genus Betacoronavirus , that could affect birds, humans, and other mammals. The WHO has described the novel coronavirus disease as COVID-19(1).

Objective: We have conducted this review to focus on the studies that assessed the treatment efficacy and safety of Coronavirus (COVID-19) and describe its relationship with the clinical outcomes of patients.

Method: PubMed, was searched for studies on the clinical evaluation of selected currently used treatments for COVID-19. We included six studies about therapeutic activity of chloroquine/hydroxychloroquine, two case series about oseltamivir and three studies about lopinavir/ritonavir

Results: Some of studies have been demonstrated and approved for a wider use of hydroxychloroquine for COVID-19, others showed that there was insufficient evidence to recommend the the routine use of this drug in patients admitted to the intensive care unit (ICU). Other treatments have insufficient evidence to recommend the use (lopinavir-Ritonavir or oseltamivir) for COVID-19 outside of research studies.

Conclusion: In order to determine efficacy and safety of chloroquine/hydroxychloroquine for COVID-19, more randomized clinical trials are required. Ideally, these studies should be double-blinded and conducted in a range of settings.

Keywords: Covid-19, hydroxychloroquine, Azithromycin, Oseltamivir, lopinavir-Ritonavir.

Introduction:

Corona virus 2019 (COVID-19) pandemic represents a global unprecedented healthcare crisis(1). Coronavirus is an enveloped RNA virus, from the genus Betacoronavirus This novel Betacoronavirus is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) based on its genetic proximity, it likely originated from bat-derived coronaviruses with spread via an unknown intermediate mammal host to humans (1). The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) presents a challenge to identify effective drugs for prophylaxis and treatment. No proven effective therapies for this virus currently exist (2). But more than 80 clinical trials have been done to test coronavirus treatments, including some drug repurposing or repositioning for COVID-19 (3).

Methods:

A literature review was performed using PubMed to identify relevant English-language articles Search terms included coronavirus, SARS-CoV-2, and COVID-19 in combination with treatment and clinical evaluation. Additional relevant articles were identified from the review of citations referenced. we included six studies about therapeutic activity of chloroquine/ hydroxychloroquine, two case series about oseltamivir and three studies about lopinavir/ritonavir

Results:

Review of Selected Repurposed Drugs

Chloroquine and Hydroxychloroquine / Azithromycin

Chloroquine (CQ) and its derivative, hydroxychloroquine (HCQ), have a long history for use as prophylactic measures in malaria-endemic regions and as treatments for autoimmune diseases with eye damage after long-term use the most common side effect (4). Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification (2). They also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells (2). Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC50) in the low micromolar range (2).

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Hydroxychloroquine has in vitro activity with a lower EC50 for SARS-CoV-2 compared with chloroquine (2). The first study reported by *Gautret et al*. (5) is a prospective open-label non-randomized clinical trial to evaluate the role of hydroxychloroquine on respiratory viral loads. Patients with confirmed COVID-19 infection were enrolled and included in a single arm protocol, to receive 600mg of hydroxychloroquine daily . Their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Azithromycin was added to the treatment depending on their clinical presentation.The end point was presence and absence of virus at day 6-post inclusion. A significant reduction of the viral carriage at day 6-post inclusion was found in 20 cases were treated in this study compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. This was significantly more efficient for virus elimination when azithromycin was added to hydroxychloroquine. *Gautret et al*. (5) reported a 100% viral clearance in nasopharyngeal swabs in 6 patients after 5 days of the combination of hydroxychloroquine and azithromycin This rate of viral clearance was lower with hydroxychloroquine alone (57.1%) and was only 12.5% in patients who did not receive hydroxychloroquine ($p< 0.001$). *Gautret et al.* (6) in another observational study assessed disease progression, and the need for oxygen or intensive cure unit (ICU) admission, They noted a clinical improvement in all 80 in-patients receiving a combination of hydroxychloroquine and azithromycin apart from one 86-year-old patient who died and one 74-year-old patient who was still in intensive care unit by the end of the study. A rapid fall of nasopharyngeal viral load was noted, with 83% negative at day 7, and 93% at day 8 and virus cultures from patient respiratory samples were negative in 97.5% patients at day 5. This allowed patients tobe rapidly discharge from highly contagious wards with a mean length of stay of five days.

Viral load and presence of SARS-CoV-2 at day 7 by (nasopharyngeal swab):

In contrast, when *Chen J et al* (7) in a pilot study tested viral load (nasopharyngeal swab) presence of SARS-CoV-2 at day 7. thirty treatment-naive patients with confirmed COVID-19 were enrolled in the study . And they found one patient in hydroxychloroquine group developed to 'severe 'during the treatment. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the hydroxychloroquine group and 14 (93.3%) cases in the control group ($P>0.05$). The median duration from hospitalization to virus nucleic acid negative conservation was 4 (range:1-9) days in hydroxychloroquine group, which is comparable to that in the control group [median 2 days (range1-4) days, ($U=83.5$, $P>0.05$)].After hospitalization, the results of median time for body temperature normalization in hydroxychloroquine treatment group was 1 (range:0-2), which was also comparable to that in the control group 1 (range:0-3). In contrast with radiological progression ,it was shown on CT images in five cases (33.3%) of the hydroxychloroquine group and seven cases (46.7%) of the control group, ehrer all patients showed improvement in follow-up examination. Four cases (26.7%) of the hydroxychloroquine group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function ($P>0.05$). *Molina et al*. (8) assessed in a prospective study virologic and clinical outcomes of 11 consecutive patients who received hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg Day 1 and 250 mg days 2 to 5) using the same dosing regimen reported by *Gautret et al*. (5). There were 7 men and 4 women with a mean age of 58.7 years (range 20-77). At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. Within 5 days, one patient died, and two were transferred to the intensive care unit. The hydroxychloroquine and azithromycin treatment were discontinued in one patient after four days because of a prolongation of the QT interval from 405 milliseconds before treatment to 460 and 470 millisecondss under the combination. Repeated nasopharyngeal were done in 10 patients (not done in the patient who died) using a qualitative PCR assay, at days 5 to 6 after treatment initiation 8/10 patients were still positive for SARS-CoV2 (80%, 95% confidence interval 49-94). In contrast with these virologic results reported by *Gautret et al*. and cast doubts about the strong antiviral efficacy of this combination. Furthermore, *Gautret et al* in their report also reported one death and three transfers to the intensive care unit among the 26 patients who received hydroxychloroquine, also underlining the poor clinical outcome with this combination. In another study which included 181 patients with SARS-CoV-2 pneumonia reported by *Mahévas et al.* (9), all were adults in four French hospitals with documented SARS-CoV-2 pneumonia and requiring oxygen ≥ 2 L/min to emulate a target trial aimed at assessing the effectiveness of hydroxychloroquine at 600 mg/day. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause. Analyses were adjusted for confounding factors by inverse probability of treatment weighting. Eighty four patients received hydroxychloroquine within 48 hours of admission (hydroxychloroquine group) while 97 did not (no- hydroxychloroquine group). the Initial severity was well balanced between the two groups. In the weighted analysis, 20.2% of patients in the hydroxychloroquine group were transferred to the ICU or died within 7 days vs 22.1% in the no-hydroxychloroquine group (16 compared with 21 events, relative risk [RR] 0.91, 95% CI 0.47–1.80). In the hydroxychloroquine group, 2.8% of the patients died within 7 days compared with 4.6% in the no-hydroxychloroquine group (3 vs 4 events, RR 0.61, 95% CI 0.13–2.89), while 27.4% and 24.1% respectively developed acute respiratory distress syndrome within 7 days (24 vs 23 events, RR 1.14, 95% CI 0.65-2.00). Eight patients receiving hydroxychloroquine (9.5%) experienced electrocardiogram modifications requiring

hydroxychloroquine discontinuation. the results of this study do not support the use of hydroxychloroquine in patients hospitalized for documented SARSCoV-2-positive hypoxic pneumonia. *Chen Z et al.* (10) evaluated the efficacy of hydroxychloroquine in the treatment of patients with COVID-19. Sixty two patients with confirmed COVID-19 were diagnosed and admitted to Renmin Hospital of Wuhan University. All patients were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day hydroxychloroquine (400 mg/d) treatment, Time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of hydroxychloroquine . Of the 46.8%. of the 62 patients enrolled in the study 29 (46.8%) were males and 33 (53.2%) were females, the mean age was 44.7 +_15.3 years. No difference in the age and sex distribution was found between the control group and the hydroxychloroquine group. The time to clinical recovery, the body temperature recovery time and the cough remission time were significantly shortened in the hydroxychloroquine treatment group. There was a larger proportion of patients with improved pneumonia in the hydroxychloroquine treatment group (80.6%, 25 of 31) compared to the control group (54.8%, 17 of 31). In the control group all four patients progressed to severe illness. However, there were two patients with mild adverse reactions in the hydroxychloroquine treatment group. Among patients with COVID-19, the use of HCQ could significantly shorten Time to clinical recovery and promote the absorption of pneumonia. Clinical efficacy of oseltamivir in treatment of Coronavirus (COVID-19) pandemic. Oseltamivir is an antiviral neuraminidase inhibitor drug ,used in the treatment and prophylaxis of infection with influenza viruses A (including pandemic H1N1) and B. It exerts its antiviral effect by inhibiting the activity of the viral neuraminidase enzyme found on the surface of the virus, which prevents budding from the host cell, viral replication, and infectivity (11). Oseltamivir is designed to be highly specific to the influenza virus and due to this high specificity, it is extremely unlikely that oseltamivir would be effective at treating the coronavirus. Independent laboratory testing conducted by Hong Kong University, School of Public Health demonstrates that oseltamivir does not have any antiviral effect on the novel coronavirus (11). Two Retrospective Case Series COVID-19 Infection studies have stated the use of oseltamivir in patients hospitalized with confirmed COVID-19 in Wuhan, China. (12), (13). In a Lancet publication describing 41 patients, 38 patients were empirically treated upon hospital admission with oseltamivir 75 mg twice daily along with antibiotic therapy (14). Common presenting symptoms in these patients included fever, cough, and myalgia or fatigue. All patients had pneumonia and abnormalities in chest CT images. The median time from onset of symptoms to hospital admission (n=41) was 7 days (range, 4-8). The median time from onset of symptoms to ICU admission (n=16) was 10.5 days (range, 8-17). Oseltamivir treatment was administered in 12 of the 13 patients, who received ICU care, and in 26 of the 28 patients, who did not receive ICU care. There was no statistical difference between the proportion of oseltamivir-treated patients admitted to the ICU compared Last Published Date: 14-04-2020 with oseltamivir-treated patients not admitted to the ICU (92% vs. 93%, p=0.46). This case series was expanded with an additional 58 cases.Three among the total of 99 patients, 75 patients received antiviral treatment including oseltamivir 75 mg every 12 hours, ganciclovir IV 0.25 g every 12 hours, and lopinavir and ritonavir tablets 500 mg twice daily. The duration of antiviral treatment was 3-14 days. No additional information on outcomes for patients who received or did not receive antiviral treatment was reported in the publication. In a *JAMA* publication, 138 patients with COVID-19 were admitted to the hospital with a median time of 7 days from the onset of symptoms (14). Of the 138 patients, 124 patients received oseltamivir. The dose of oseltamivir was adjusted based on the severity of the disease and was not reported. The authors noted that no effective outcomes were observed. Ongoing Trial Information: Tamiflu in combination with other medications are currently being studied in clinical trials for the treatment of COVID-19. For additional information on these trials (table 1) (15).

Table (1) Ongoing clinical studies about oseltamivir

Study Identifier	Treatment	Study Population	Estimated Study Completion
NCT04303299	Various combination of protease inhibitors, oseltamivir, favipiravir, and chloroquin	Patients with mild to severe COVID-19	November 30, 2020
NCT04261270	ASC09F + oseltamivir vs Ritonavir + oseltamivir vs oseltamivir	Patients with non-severe COVID-19	July 1, 2020
NCT04255017	Abidol hydrochloride vs Oseltamivir vs Lopinavir/ritonavir	Patients with mild to severe COVID-19	July 1, 2020
NCT04338698	Hydroxychloroquine vs a series of combinations of hydroxychloroquine, oseltamivir and azithromycin	Patients with COVID-19	November 30, 2020

Lopinavir–Ritonavir in treatment of Coronavirus (COVID-19) pandemic. Aspartyl protease is an enzyme encoded by the pol gene of the human immunodeficiency virus (HIV) that cleaves the precursor polypeptides in HIV, thus playing an essential role in its replication cycle(16). The HIV protease inhibitors, lopinavir and ritonavir, are therefore used in combination as HIV therapeutic drugs(17). Although coronaviruses encode a different enzymatic class of protease, the cysteine protease, theoretical evidence exists that lopinavir and ritonavir also inhibit the action of the enzyme 3-chymotrypsin-like protease ($3CL^{pro}$), thereby disrupting the process of viral replication and release from host cells (16), (17). *Cao et al* conducted an open-label retrospective clinical trial at a single hospital in Wuhan, China (18)which enrolled a total of 199 patients with laboratory-confirmed SARS-CoV-2 infection Randomization assigned 99 patients were assigned to the lopinavir-ritonavir group, and 100 patients to the standard-care group .The results (hazard ratio for clinical improvement 1.31, 95% confidence interval [CI], 0.95 to 1.80)in dicated that treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement The percent mortality at 28 days was similar in two study groups the lopinavir-ritonavir group and the standard-care group (19.2% vs. 25.0%, respectively difference -5.8, percentage points 95% CI, -17.3 to 5.7). In contrast with percentages of patients with detectable viral RNA at various time points, were similar. The conclusion of this clinical trial, lopinavir-ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care group with (hazard ratio, 1.39, 95% CI, 1.00 to 1.91). Safety of lopinavir-ritonavir treatment in Confirmed COVID-19 patients. Adverse events were also reported in above mentioned clinical trial, the results were 46 patients (46.5%) in the lopinavir- ritonavir group and 49 patients (49%) in the standard care group reported adverse events between randomization and day 28. In the lopinavir–ritonavir group the gastrointestinal while serious adverse events were more common, and serious adverse events were more common in the standard-care group. The treatment of lopinavir–ritonavir was stopped early in 13(13.8%) patients because of adverse events. The *ELACOI* (19) trial, a single-blind randomized controlled trial, was also performed in China, in which 44 laboratory-confirmed SARS-CoV-2 patients was enrolled. Patients with mild or moderate clinical status (with or without signs of pneumonia) were suitable for inclusion. The mean age was 49.4 years (range 27-79). Twenty-one participants were randomized to receive lopinavir- ritonavir for 14 days, 16 to receive Umifenovir (another antiviral) and seven to standard care with no antiviral. The results there was no difference in the primary outcome of time to negative pharyngeal SARS-CoV-2 PCR test between the lopinavir, Umifenovir and control groups (8.5 (IQR 3-13), 7 (IQR 3-10.5) and 4 (IQR 3-10.5) days, respectively). There were no differences in pyrexia, cough or lung CT findings at 7 and 14 days. In the lopinavir- ritonavir arm, 38.1% deteriorated to severe/critical clinical status, compared to 12.5% in the Umifenovir arm and 14.3% in the control arm (p=0.186). Five patients in the lopinavir- ritonavir group experienced adverse events (gastrointestinal and deranged liver function), whilst no adverse events occurred in the Umifenovir or control groups. Another clinical trial of 120 patients in China, (20) 78 patients (65%) recieved lopinavir- ritonavir treatment and were categorized as severe COVID-19 . they had a higher ratio of lymphocyte count <0.8×109/liter than those without lopinavir- ritonavir treatment. Of then78 patients who received lopinavir- ritonavir treatment, 16 patients (20.5%), 46 (59%) and 64 (82.1%) were initially administered lopinavir-ritonavir treatment within 5 days, 10 days and 15 days from symptom onset, respectively. Seven patients (8.9%) started to recieve lopinavir- ritonavir treatment after 20 days. The median duration of lopinavir- ritonavir treatment was 10 days (IQR 9-10). Sixty one patients (78.2%) received ≥10 days LRV/r treatment. The median duration of SARS-CoV-2 shedding in lopinavir- ritonavir treatment group was 22 days (IQR 18-29), which was shorter than that in no LPV/r treatment group (28.5 days, IQR 19.5-38) (p=0.02). Patients who started lopinavir-ritonavir treatment within 10 days from symptom onset had a shorter duration of SARS-CoV-2 RNA shedding than other patients who began after 10 days (median 19 days vs. 27.5 days, p<0.001). In contrast, the median duration of viral shedding did not differ between patients who initiated lopinavir- ritonavir treatment from symptom onset >10 days and patients who did not receive lopinavir- ritonavir treatment (median 27.5 days vs. 28.5 days, p=0.86). Suggesting that lopinavir- ritonavir treatment ≤10 days from symptom onset reduced the duration of viral shedding. Ongoing trial on a combination of lopinavir- ritonavir, ribavirin and interferon beta-1b (21) will expedite the recovery, suppress the viral load, shorten hospitalization and reduce mortality in patients with 2019-n-CoV infection . lopinavir-ritonavir patients will be randomly assigned to either a 14-day course of lopinavir- ritonavir 400mg/100mg twice daily, ribavirin 400mg bd and zero to three doses of subcutaneous injection of interferon beta-1b 1mL (0.25mg; 8 million IU) on day 1, 3 and 5 (depending on day of admission from symptoms onset) plus standard care, or a 14-day course of lopinavir- ritonavir 400mg/100mg twice daily plus standard care alone (2:1).

Conclusion:

We present a review of the current studies that state of knowledge on the COVID-19 pandemic, most of them are based on repurposing the therapeutic agents previously designed for other applications. The limitations of the current review may be summarized by the inclusion of English-language articles only and the lack of sufficient clinical trials about the selected drugs. In conclusion, as for now, some of the studies about chloroquine/ hydroxychloroquine have already

demonstrated promising results and so these agents have been approved for a wider use,while other studies concluded that there was insufficient evidence to offer any recommendation on the routine use of these drugs especially in patients admitted to the intensive care unit (ICU). Meanwhile there is insufficient evidence to recommend the use of lopinavir- ritonavir or oseltamivir for COVID-19 outside of research studies. In order to determine their efficacy and safety for COVID-19, more adequately powered randomized clinical trials are required.

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