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COVID-19

Systematic and Statistical Review of Coronavirus Disease 19 Treatment Trials

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Abstract

The following systematic review and meta-analysis compile the current data regarding human controlled COVID-19 treatment trials. An electronic search of the literature compiled studies pertaining to human controlled treatment trials with COVID-19. Medications assessed included lopinavir/ritonavir, arbidol, hydroxychloroquine, tocilizumab, favipiravir, heparin, and dexamethasone. Statistical analyses were performed for common viral clearance endpoints whenever possible. Lopinavir/ritonavir showed no significant effect on viral clearance for COVID-19 cases (OR 0.95 [95% CI 0.50–1.83]). Hydroxychloroquine also showed no significant effect on COVID-19 viral clearance rates (OR 2.16 [95% CI 0.80–5.84]). Arbidol showed no 7-day (OR 1.63 [95% CI 0.76–3.50]) or 14-day viral (OR 5.37 [95% CI 0.35–83.30]) clearance difference compared to lopinavir/ritonavir. Review of literature showed no significant clinical improvement with lopinavir/ritonavir, arbidol, hydroxychloroquine, or remdesivir. Tocilizumab showed mixed results regarding survival. Favipiravir showed quicker symptom improvement compared to lopinavir/ritonavir and arbidol. Heparin and dexamethasone showed improvement with severe COVID-19 cases requiring supplemental oxygenation. Current medications do not show significant effect on COVID-19 viral clearance rates. Tocilizumab showed mixed results regarding survival. Favipiravir shows favorable results compared to other tested medications. Heparin and dexamethasone show benefit especially for severe COVID-19 cases.

Keywords COVID-19 · SARS-CoV2 · Coronavirus · Treatment · Trials · Lopinavir/ritonavir · Arbidol · Hydroxychloroquine · Remdesivir · Tocilizumab · Favipiravir · Heparin · Dexamethasone

Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) is a novel coronavirus responsible for causing coronavirus disease 19 (COVID-19). It quickly became a pandemic in the beginning of 2020. Originating in Wuhan, China, the virus rapidly spread to other countries of the world [1]. On January 30, 2020, the World Health Organization (WHO) declared SARS-CoV2 a Public Health Emergency of International Concern (PHEIC) [2]. Medications are quickly being tested to assess for a suitable treatment regimen for the novel virus. The following systematic and statistical review assesses the current evidence regarding human controlled COVID-19 treatment trials.

This article is part of the Topical Collection on *Covid-19*

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Methods

Data Collection

An electronic search compiled human controlled studies analyzing treatments for COVID-19. Medical therapies investigated included lopinavir/ritonavir, arbidol, hydroxychloroquine, remdesivir, favipiravir, heparin, glucocorticoids, interferon, ivermectin, and convalescent plasma. Inclusion criteria included needing a control (whether standard therapy, placebo, or another medication) and testing among human subjects with COVID-19. In vitro and animal studies plus those without controls were not included in the review.

Databases included Google Scholar and Pubmed. Key words included COVID-19, SARS-CoV2, randomized,

controlled, human, retrospective, prospective, trial, chloroquine, hydroxychloroquine, lopinavir, ritonavir, arbidol, umifenovir, tocilizumab, favipiravir, steroids, dexamethasone, glucocorticoids, interferon, ivermectin, remdesivir, azithromycin, heparin, and low-molecular weight heparin. Abstracts and titles were reviewed for relevancy. Studies that had human subjects and a control arm were included in the study; otherwise, they were excluded. Duplicated studies were removed. The studies were organized based on the study medication; some studies presented more than one study medication and were included in more than one group. Statistical analysis was performed if there were two or more studies showing information regarding positive-to-negative conversion rates; number of days varied based on reported similarities among chosen studies.

Statistical Analysis

If there were any common endpoints among the trials collected, a meta-analysis would then be performed. Endpoints were related to viral clearance. Statistical analyses used the Review Manager Version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) software program. A forest plot was created using the program with the DerSimonian and Laird fixed-effects model to reduce heterogeneity. The mean difference with a confidence interval (CI) of 95% was reported with the inverse variance method. Due to using a scale, the value marking no significance via confidence interval was zero. An I^2 greater than 50% suggests significant heterogeneity. If there was significant heterogeneity, a random-effects model would be used instead.

Results

Study Selection

A total of 1781 articles were found with the keywords selected. A total of 57 studies were included initially based on title and abstract review. A total of 26 studies were included in the systematic review: Four studies elaborated about lopinavir/ritonavir; four studies studied arbidol, six for hydroxychloroquine, one for remdesivir, six for tocilizumab, two for favipiravir, two for heparin, and one for dexamethasone. Statistical analyses regarding positive-to-negative conversion rates were possible for lopinavir/ritonavir, arbidol, and hydroxychloroquine. No human controlled trials were found for glucocorticoids, interferons, ivermectin, or convalescent plasma. Statistical analysis regarding positive-to-negative conversion rates was possible for lopinavir/ritonavir (two studies), arbidol (two studies), and hydroxychloroquine (four studies) (Fig. 1).

Lopinavir/Ritonavir

Treatment

Four controlled trials exist regarding the treatment for COVID-19 (Table 1). Two studies are randomized controlled trials and two are retrospective controlled studies [3–6].

The most recognized is the randomized, controlled, open-label trial by Cao et al. [3] The study showed no significant difference in terms of 28-day mortality or time of positive-to-negative reverse transcriptase-polymerase chain reaction (RT-PCR) conversion. Lopinavir-ritonavir did reduce the time to clinical improvement by 1 day but was considered marginally non-statistically significant. This study had many limitations. The study was organized as an open label and with lack of placebo. About 14% of trial recipients could not complete a full 14-day treatment course due to adverse medication effects including nausea, vomiting, and diarrhea. However, the incidence of respiratory failure, acute kidney injury, and secondary infection was higher in the standard-care group.

Positive-to-negative RT-PCR conversion was not significant with lopinavir-ritonavir (Fig. 2) [3, 4]. There was no significant difference between the study and control group at 14 days (OR 0.95 [95% CI 0.50–1.83]). Other retrospective studies suggest earlier clearance with lopinavir-ritonavir but did not report the results at 14 days [5, 6]. Furthermore, the two studies that did suggest clearance are retrospective studies while the other two are randomized controlled trials.

Adverse Effects

The most significant lopinavir/ritonavir side effects include loss of appetite, nausea, vomiting, and diarrhea [3, 4]. Diarrhea can possibly become severe [4]. Apart from elevated transaminase levels, other laboratory markers do not significantly differ from the control group [3, 4].

Umifenovir (Arbidol)

Treatment

There are currently four controlled trials discussing the use of arbidol for the treatment of COVID-19 patients (Table 2) [4, 7–9]. Two of the trials are randomized while the other two are retrospective studies. Only Li et al. includes a comparison between arbidol and standard supportive therapy [4]. The two retrospective studies include a comparison with lopinavir/ritonavir [8, 9]. Chen et al. compare arbidol with favipiravir [7].

Arbidol was commonly compared with lopinavir/ritonavir [4, 9] while there is no difference in positive-to-negative conversion rates between the two medications at the seventh (OR 1.63 [95% CI 0.76–3.50]) or 14th day (OR 5.37 [95% CI 0.35–83.30]) (Figs. 3 and 4). Of note, for the 14-day comparison, a fixed effect

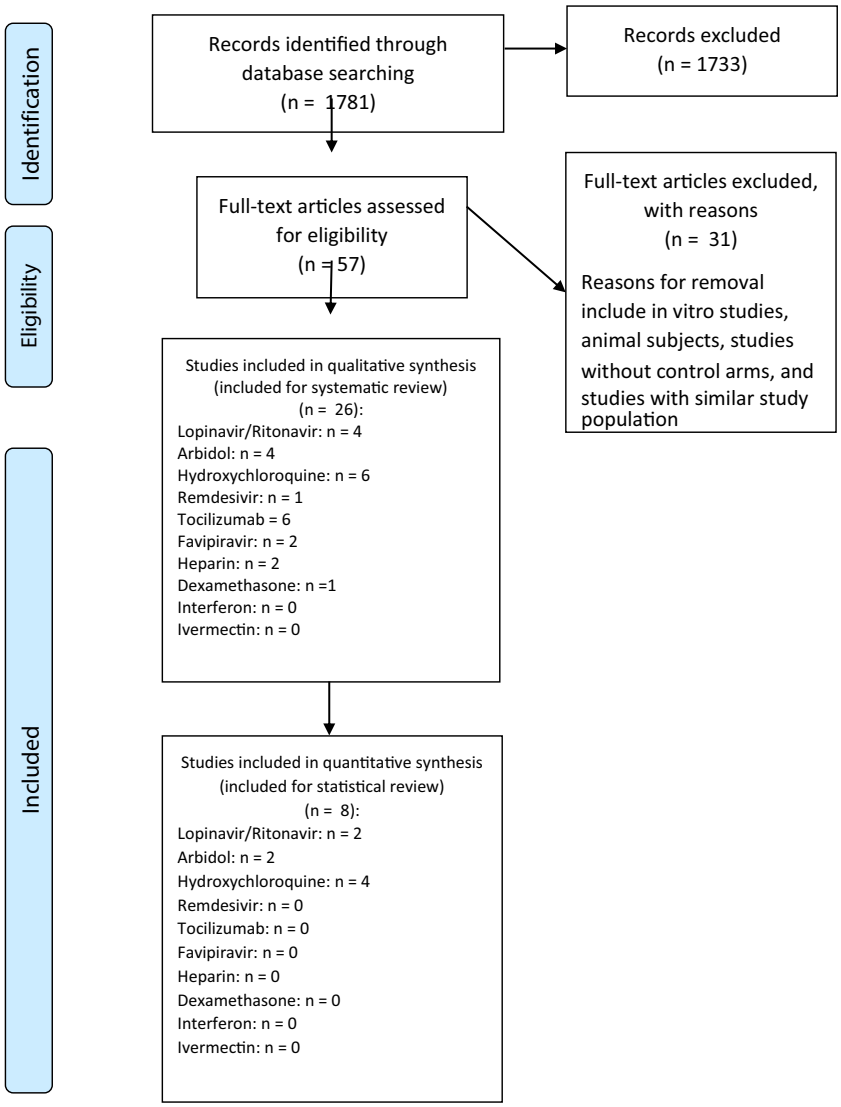

Fig. 1 PRISMA flowchart revealing study selection process

model would show arbidol having more viral clearance compared to lopinavir/ritonavir (OR 5.0 [95% CI 1.50–16.64]). However, there was significant heterogeneity between the two studies ($I^2 = 66\%$). A random effects model was therefore

Table 1 Characteristics of lopinavir/ritonavir studies for COVID-19

Study	Type	Number of patients	Findings
Cao et al. 2020 [3]	Randomized	199 $T = 99$ $C = 100$	No significant difference in 28-day mortality, positive-to-negative RT-PCR conversion, or time to clinical improvement
Li et al. 2020 [4]	Randomized	28 $T = 21$ $C = 7$	No significant difference in positive-to-negative RT-PCR conversion or time to clinical improvement
Ye et al. 2020 [5]	Retrospective	47 ($T = 42$; $C = 5$)	Symptoms and labs improved earlier for lopinavir/ritonavir group. Positive-to-negative RT-PCR conversion also decreased with lopinavir/ritonavir.
Yan et al. 2020 [6]	Retrospective	120 $T = 78$ $C = 42$	Symptoms improved earlier for lopinavir/ritonavir group. Positive-to-negative RT-PCR conversion also decreased with lopinavir/ritonavir.

T, treatment group (lopinavir/ritonavir); *C*, control group

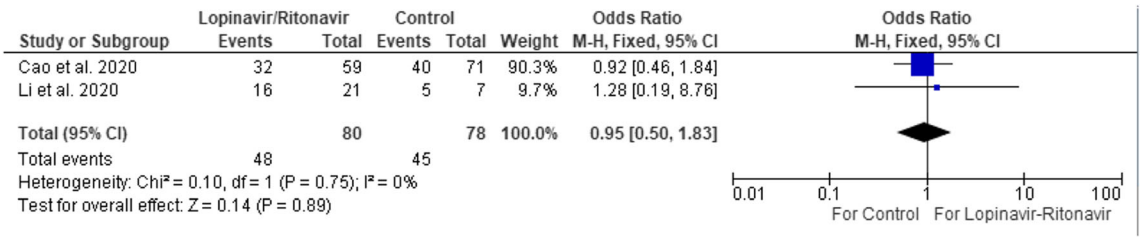

Fig. 2 Positive-to-negative RT-PCR conversion of lopinavir/ritonavir versus control at 14 days

employed to counter the heterogeneity, resulting in a nonsignificant difference between the two medications.

Adding arbidol with lopinavir/ritonavir did show significant conversion rates and CT scan improvements compared to lopinavir/ritonavir by itself [8].

While favipiravir did not show any difference compared to arbidol regarding 7-day recovery rate, it did show faster recovery from fever and cough. There was no difference regarding oxygen and non-invasive positive pressure ventilation use between arbidol and favipiravir [7].

Adverse Effects

Arbidol side effects include nausea and diarrhea [4]. Arbidol demonstrated less hyperuricemia compared to favipiravir ($p = 0.0014$). Both favipiravir and arbidol did not show any significant difference in abnormal liver function tests, psychiatric symptom reaction, or digestive tract reactions [7].

Hydroxychloroquine

Treatment

Six controlled trials exist comparing hydroxychloroquine versus standard therapy (Table 3) [10–15]. Three studies were randomized, one was prospective, and two were retrospective studies.

The data regarding hydroxychloroquine remains equivocal. The three randomized controlled trials present conflicting information regarding significance in clinical improvement and positive-to-negative conversion [10, 11, 13]. Chen Z et al. observed conversion based on CT scan results, but CT scans have a high negative predictive value for COVID-19 during the pandemic [16–19]. The prospective trial by Gautret et al. showed earlier conversion with hydroxychloroquine [12]. They included patients that took azithromycin with hydroxychloroquine in their study, but that was not included in this analysis. They have yet to present clinical status changes from their study.

A retrospective controlled study among veterans showed increased mortality with hydroxychloroquine use. Mechanical ventilation rates were similar among the two study arms [14]. Another retrospective review showed no difference in in-hospital mortality [15].

The positive-to-negative conversion analysis (Fig. 5) was performed at 6–7 days to include all the studies. RT-PCR or CT scans were used to monitor time to COVID-19 resolution. Hydroxychloroquine did not show significant effects on positive-to-negative conversion time compared to standard therapy (OR 2.16 [95% CI 0.80–5.84]). With significant heterogeneity ($I^2 = 56\%$), a random-effects model was used.

Table 2 Characteristics of arbidol studies for COVID-19

Study	Type	Control medication	Testing medication	Patients	Findings
Chen C et al. 2020 [7]	Randomized	Favipiravir	Arbidol	236 $T = 116$ $C = 120$	No difference in the 7-day clinical recovery rate between favipiravir and arbidol. Favipiravir decreases the time to fever and cough resolution.
Deng L et al. 2020 [8]	Retrospective	LPV/r	LPV/r + arbidol	33 $T = 16$ $C = 17$	Dual therapy with LPV/r and arbidol showed better 7- and 14-day negative conversion rates and more 7-day chest CT scan improvements compared to LPV/r alone
Zhu Z et al. 2020 [9]	Retrospective	LPV/r	Arbidol	50 $T = 16$ $C = 34$	Arbidol had shorter duration of positive RNA tests compared to LPV/r
Li Y et al. 2020 [4]	Randomized	No anti-viral therapy	Arbidol	52 $T = 35$ $C = 17$	Positive-to-negative conversion rates and CT scan clearance rates were similar between arbidol and the control group at 7 and 14 days.

T, testing group; *C*, control group; *LPV/r*, lopinavir/ritonavir

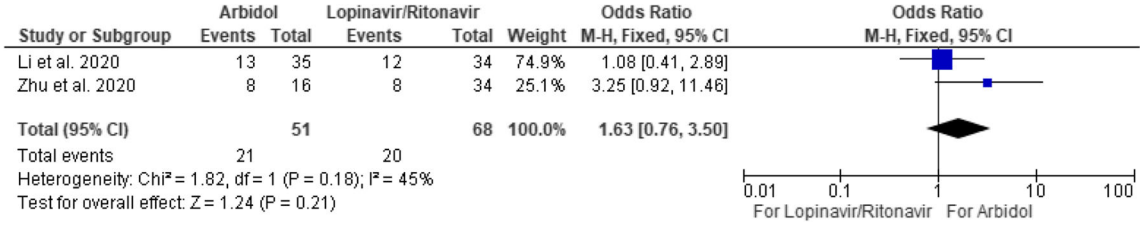

Fig. 3 Positive-to-negative RT-PCR conversion of arbidol versus lopinavir/ritonavir versus at 7 days

Analyzing the three randomized controlled trials only showed no significant difference between hydroxychloroquine and standard therapy (OR 1.50 [95% CI 0.88–2.57]) (Fig. 6) [10, 11, 13]. This was with nonsignificant heterogeneity (I^2 = 38%), and therefore a fixed-effects model was kept.

Adverse Effects

Cardiac complications, including cardiac arrest, were more common with hydroxychloroquine use especially when combined with azithromycin [15]. Gastrointestinal symptoms, including diarrhea and elevated transaminase levels, were mentioned with hydroxychloroquine, but they were not statistically significant compared to the control groups [11, 12, 14].

Remdesivir

Treatment

Currently there is only one published controlled trial with remdesivir (Table 4) [20]. The randomized, double-blind, placebo-controlled trial showed no difference in time to clinical improvement compared to the control arm (hazard ratio 1.23 [95% CI 0.87–1.75]) [20]. A limitation of the study however was that patients in both groups were permitted concomitant use of lopinavir-ritonavir, interferons, and/or corticosteroids.

Adverse Effects

About 66% who received remdesivir reported an adverse side effect. The most common side effects were constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased bilirubin [20].

Tocilizumab

Treatment

Six studies assessed the benefits of tocilizumab (Table 5). Tocilizumab presents with mixed results. Half of the studies report no significant benefit compared to standard therapy [21–23], while the other half report improvement for severe cases or improved hospital stay, survival, and freedom from ventilation [24–26]. No studies assessed the duration of positive-to-negative SARS-CoV2 conversion.

Adverse Reactions

The following studies did not report any associated side effects with tocilizumab compared to standard therapy.

Favipiravir

Treatment

There are two controlled trials regarding the use of favipiravir (Table 4) [7, 27]. The first is a randomized controlled trial comparing favipiravir to arbidol for COVID-19 patients [7]. Arbidol effects are similar to standard therapy [4]. The other is an open-label, non-randomized, prospective trial comparing favipiravir versus lopinavir/ritonavir [27]. Lopinavir/ritonavir is also similar to standard therapy [3, 4] (Table 6).

Chen et al. showed no significant 7-day recovery rate with favipiravir compared to arbidol. The secondary endpoints of fever and cough relief did resolve significantly sooner with favipiravir compared to arbidol, with fever resolving for all patients at day 4 (versus days 7–8) and cough improving at day 8 (versus day 8+). There was no difference regarding oxygen and non-invasive positive pressure ventilation use [7].

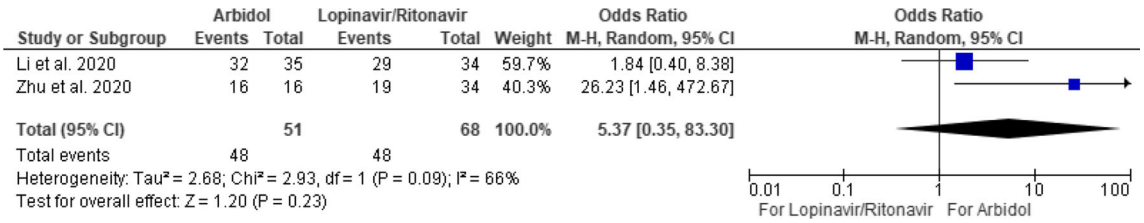

Fig. 4 Positive-to-negative RT-PCR conversion of arbidol versus lopinavir/ritonavir versus at 14 days

Table 3 Characteristics of hydroxychloroquine studies for COVID-19

Study	Type	Patients	Method of surveillance	Findings
Chen Z et al. 2020 [10]	Randomized	62 $T = 31$ $C = 31$	CT scan at day 6	Hydroxychloroquine presented with earlier clinical improvement and positive-to-negative CT scan conversion
Chen J et al. 2020 [11]	Randomized	30 $T = 15$ $C = 15$	RT-PCR at d ay 7	No significant difference in clinical improvement and positive-to-negative RT-PCR conversion
Gautret et al. 2020 [12]	Prospective	30 $T = 14$ $C = 16$	RT-PCR at day 6	Hydroxychloroquine presented with earlier positive-to-negative RT-PCR conversion
Tang et al. 2020 [13]	Randomized	150 $T = 75$ $C = 75$	RT-PCR at day 7	No significant difference in positive-to-negative RT-PCR conversion, symptom improvement, or laboratory value improvements.
Magagnoli et al. 2020 [14]	Retrospective	368 $T = 210$ $C = 158$	No surveillance	Hydroxychloroquine had an increased mortality rate. Ventilator use was similar.
Rosenberg et al. 2020 [15]	Retrospective	1227 $T = 1006$ $C = 221$	No surveillance	No difference in in-hospital death, but hydroxychloroquine caused more cardiac complications.

T treatment group (hydroxychloroquine); *C* control group

Cai et al. showed faster CT scan improvement and viral clearance with favipiravir compared to lopinavir/ritonavir. At day 14, 32/35 (91.43%) favipiravir subjects had improved chest CT scans compared to 28/45 (62.22%) lopinavir/ritonavir patients ($p = 0.004$). Viral clearance was sooner at 4 days with favipiravir compared to 11 days with lopinavir/ritonavir ($p < 0.001$) [27].

Adverse Effects

Favipiravir shows a similar side-effect profile as to lopinavir/ritonavir, including nausea, vomiting, diarrhea, rash, and elevated transaminase levels [7, 27]. Compared to arbidol, it increases uric acid levels more. While the side effect profile is similar to lopinavir/ritonavir, the frequency of adverse effects is less with favipiravir [27].

Unfractionated and Low-Molecular Weight Heparin

Treatment

Two retrospective controlled studies included data regarding heparin use (Table 5) [28, 29]. These studies involved deep vein thrombosis prophylaxis dosing of unfractionated (15,000 IU/day) and low-molecular weight (40–60 mg/day) heparin (Table 7).

Tang et al. showed no difference in 28-day mortality rates. Most patients received low-molecular weight heparin. They note significant improvement in heparin users among those with severe sepsis-induced intravascular coagulopathy. This was determined by a scoring system utilizing platelet count, prothrombin time, and Sequential Organ Failure Assessment (SOFA) scoring [28].

Shi et al. showed no difference in outcomes including clinical improvement and positive-to-negative conversion rate. All patients in the study improved [29].

Adverse Effects

The studies included in the review did not report adverse effects. However, all heparin medications have well-documented side-effects including hemorrhage, osteoporosis, renal tubular acidosis type 4 with hyperkalemia, and heparin-induced thrombocytopenia [30–32]. Adverse effects of low-

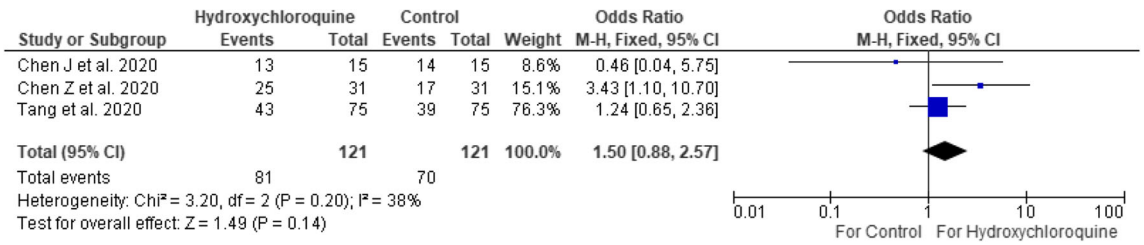

Fig. 5 Positive-to-negative conversion of hydroxychloroquine versus control at 6–7 days

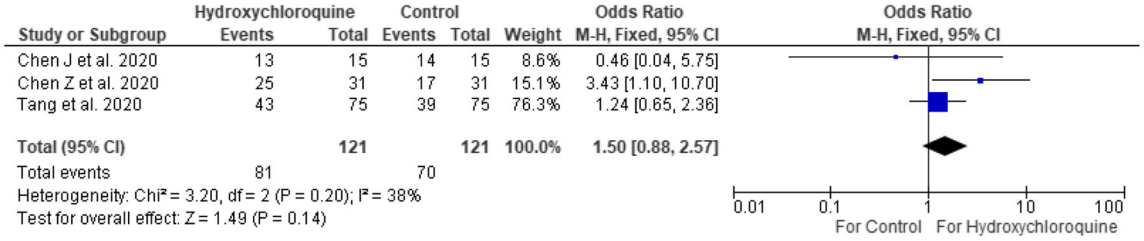

Fig. 6 Randomized controlled trials showing positive-to-negative conversion of hydroxychloroquine versus control at 6–7 days

molecular weight heparin are more common in patients with kidney injury [33]. Deep vein thrombosis prophylaxis presents with a lower rate of side-effects [34].

Dexamethasone

Treatment

One large randomized controlled trial, the RECOVERY Trial, found an overall benefit when assessing all COVID19 cases together (Table 8) [35]. While there was no benefit for those without oxygen needs, dexamethasone reduced mortality by one-fifth in patients requiring noninvasive oxygen therapy, and by one-third in those requiring mechanical ventilation. Dexamethasone also reduced hospital length of stay and progression to needing invasive mechanical ventilation.

Adverse Reactions

While the RECOVERY trial does not report any adverse reactions compared to the standard therapy, glucocorticoids have multiple side-effects. Adverse reactions from acute use include altered mental status, hyperglycemia, increased risk for infection, hypertension, arrhythmias, and myopathy [36, 37].

Discussion

Lopinavir/ritonavir, arbidol, hydroxychloroquine, favipiravir, remdesivir, and heparin are medications that have been tested in human controlled trials for COVID-19 treatment. For the meta-analyses, neither lopinavir/ritonavir nor hydroxychloroquine showed significant positive-to-negative conversion rates. The systematic review revealed inconclusive or negative results for all medications regarding clinical improvement. Favipiravir showed significant improvement compared to its competitor medications, but there were no supportive therapy or placebo-controlled trials. Heparin showed significant clinical improvement only with those with severe COVID-19. Apart from heparin, the adverse effects of the medications mainly include gastrointestinal symptoms.

Lopinavir, a HIV protease inhibitor, inhibits the major protease involved in COVID-19 replication and development of functional viral proteins. Ritonavir acts to increase the levels of lopinavir and improve bioavailability [38–40]. Lopinavir/ritonavir along with ribavirin were previously used to treat SARS in non-randomized clinical trials to prevent development of ARDS [41]. In vitro studies show an antiviral effect of lopinavir on COVID-19 [42]. However, human trials show no significant difference in clinical improvement and viral shedding. Furthermore, a comparison trial shows inferiority to arbidol regarding viral clearance [9].

While arbidol has displayed antiviral effects with previous coronaviruses [43–45], the mechanism of action on COVID-19 is currently unknown. In human trials, arbidol shows no significant positive-negative conversion rate or recovery time compared to standard therapy or lopinavir/ritonavir [4, 9]. The meta-analysis comparing 7- and 14-day viral clearance between arbidol and lopinavir/ritonavir possibly favored arbidol significantly. Employing a random-effects model to account for large heterogeneity removed the statistical significance. It does show promise for post-exposure prophylaxis [45].

Hydroxychloroquine, a member of the 4-aminoquinolines, works by neutralizing the acidic potential of lysosomes resulting in an inhibition of cell chemotaxis, phagocytosis, antigen presentation, and interferon release [46–58]. In vitro studies have shown its anti-viral effects on COVID-19, specifically by preventing viral infusion by altering the pH of cell membranes and impairing ACE2 receptor-mediated entry. It further disrupts viral activity inside the cell [48]. Combining

Table 4 Characteristics of remdesivir studies for COVID-19

Study	Type	Patients	Findings
Wang et al. 2020 [20]	Randomized	237 $T = 158$ $C = 79$	No difference with 28-day mortality, clinical improvement, and viral load change.

T, treatment group (remdesivir); *C*, control group

Table 5 Characteristics of tocilizumab studies for COVID-19

Study	Type	Patients	Findings
Colaneri et al. 2020 [21]	Prospective	42 $T = 21$ $C = 21$ (hydroxychloroquine, azithromycin, heparin DVT prophylaxis)	Tocilizumab did not reduce 7-day mortality rates.
Martinez-Sanz et al. 2020 [22]	Retrospective	1229 $T = 260$ $C = 969$	Tocilizumab had no difference in death or ICU admissions compared to the control.
Ip et al. 2020 [23]	Retrospective	547 $T = 134$ $C = 413$	Tocilizumab had no statistically significant benefit in ICU survival.
Wadud et al. 2020 [24]	Retrospective	94 $T = 44$ $C = 50$	Tocilizumab was associated with increased survival for patients requiring mechanical ventilation
Capra et al. 2020 [25]	Prospective	85 $T = 62$ $C = 23$ (hydroxychloroquine and lopinavir/ritonavir)	Tocilizumab was associated with improved in-hospital survival
Rossi et al. 2020 [26]	Retrospective	168 $T = 84$ $C = 84$	Tocilizumab was associated with improved survival and freedom from ventilation

T, treatment group (tocilizumab); *C*, control group

all the hydroxychloroquine human trials showed no benefit with reducing COVID-19 viral shedding time. Most of these studies included azithromycin. One retrospective trial suggests increase mortality with hydroxychloroquine use [14]. The ineffectiveness, high side-effect profile, and increased mortality caused researchers from the Solidarity Trial—a trial comparing the effects of hydroxychloroquine, remdesivir, lopinavir-ritonavir, and interferon-beta—to cancel their hydroxychloroquine study arm [49, 50]. There are no human trials showing the efficacy of hydroxychloroquine for COVID-19 prophylaxis. Side-effects include visual abnormalities, gastrointestinal issues, cardiac arrhythmias with QT interval prolongation, drug-induced psychosis, and leukopenia. It also interacts with various other medications, including heparin to increase the risk of the bleeding and lopinavir/ritonavir to further prolong the QT interval [51].

Remdesivir is a prodrug that is metabolized into an analogue of adenosine triphosphate, allowing it to inhibit viral RNA polymerases [52]. In vitro studies exhibit its potential in combating SARS-CoV2 [52, 53]. A cohort study suggested potential benefit as compassionate use for severe COVID-19 [53]. However, the randomized, double-blinded, placebo-controlled trial included in the review showed no statistical effect with remdesivir regarding clinical improvement, mortality, and viral load change [20]. Adverse effects were not significant among the groups. Limitations to the study included both study groups allowing for other therapies (i.e., glucocorticoids and lopinavir/ritonavir), although their use was not

Table 6 Characteristics of favipiravir studies for COVID-19

Study	Type	Control medication	Patients	Findings
Chen et al. 2020 [7]	Randomized	Arbidol	236 $T = 116$ $C = 120$	Favipiravir has no significant 7-day clinical recovery compared to arbidol. Favipiravir does have decreases the time to fever and cough resolution
Cai et al. 2020 [27]	Prospective	Lopinavir/ritonavir	80 $T = 35$ $C = 45$	Favipiravir showed more 14-day chest CT scan improvement and sooner viral clearance compared to lopinavir/ritonavir

T, treatment group (favipiravir); *C*, control group

Table 7 Characteristics of heparin studies for COVID-19

Study	Type	Patients	Findings
Tang et al. 2020 [28]	Retrospective	449 $T = 99$ $C = 350$	No difference in 28-day mortality overall, but among patients with severe sepsis-induced intravascular coagulapathy, heparin improved 28-day mortality
Shi et al. 2020 [29]	Retrospective	42 $T = 21$ $C = 21$	No difference in positive-to-negative clearance rate or duration of hospital stay

T treatment group (heparin); *C* control group

significantly different among the groups. Remdesivir was also started late in some of the study patients. The study was also considered underpowered [20].

Tocilizumab is an IL-6 antibody that suppresses acute phase reactants [54]. It shows a possible benefit for patients with COVID19. Few studies showed survival benefit plus decreased risk of ventilation and disease progression. However, other studies showed no significant benefit. More studies are required to establish the true benefit of tocilizumab.

Favipiravir is a broad spectrum antiviral against RNA viruses. Inside infected host cells, it becomes phosphorylated into favipiravir-RTP and inhibits viral RNA-dependent RNA polymerase [55, 56]. Favipiravir also suppresses tumor necrosis factor-alpha (TNF-a) production [57, 58]. The human COVID-19 trials with favipiravir are compared with two specific controls. Compared to arbidol, favipiravir reduces symptom duration [7]. Compared to lopinavir/ritonavir, favipiravir reduces viral shedding time and hastens chest CT scan improvement while having fewer side effects [27]. Favipiravir adverse effects include gastrointestinal symptoms and elevated uric acid levels [7, 27] Its safe profile has made it a preferred medical therapy for those with cardiovascular and renal disease [59, 60].

Heparin has various non-anticoagulant properties including reducing IL-6-associated inflammation [61–63]. IL-6 causes hypercoagulation [63]. Levels are significantly higher in severe COVID-19 patients [61, 64, 65]. Heparin binds to IL-6, reducing the interaction between IL-6, SIL-6R, and sgp130 [66]. This benefit may explain the meta-analysis findings showing ARDS-associated mortality benefit with early low-molecular weight heparin initiation [67]. Heparin also binds to various viral entry proteins, including herpes simplex, zika, and SARS [68–70]. Similarly, it attaches to the S1 spike protein of COVID-19 and causes a conformational change, inhibiting viral membrane fusion with the cell wall [71]. The current studies suggest benefit mainly with severe COVID-19 cases [28, 29].

Dexamethasone shows promise with decreased mortality in overall COVID-19 cases. The benefit is particularly seen with patients requiring supplemental oxygenation or mechanical ventilation. There was no benefit for mild cases. This may be due to dexamethasone suppressing the cytokine storm [72]. While only one study showed results regarding dexamethasone, it was a large, randomized controlled trial.

Limitations

The meta-analysis portion of the study has some limitations. The first limitation is the small number of patients in the trials and therefore the overall analysis. Another limitation is the use of surrogate endpoints to complete the meta-analysis. This is regarding the use of CT scan resolution for viral clearance in the hydroxychloroquine analysis. Chest CT scans have significant negative predictive value, but is not directly comparable to RT-PCR [16–19]. The endpoints were not well-established among all reviewed medications, making it difficult to compare them between studies.

Regarding the systematic review, publication bias influences the information presented. Favipiravir trials on COVID-19 only involve those compared with other

Table 8 Characteristics of dexamethasone studies for COVID-19

Study	Type	Patients	Findings
Horby et al. 2020 [35]	Randomized	6425 $T = 2104$ $C = 4321$	Dexamethasone reduced 28-day mortality, especially in those requiring any form of oxygenation.

T, treatment group (dexamethasone); *C*, control group

medications and not with a placebo or supportive therapy control arm. The heparin and dexamethasone studies mainly involved the level of severity of COVID-19 rather than having the infection itself.

Conclusion

Current investigated medications do not hasten viral clearance time. Clinical improvement is equivocal with lopinavir/ritonavir, arbidol, hydroxychloroquine, and remdesivir. Favipiravir shows faster viral clearance and clinical improvement compared to lopinavir/ritonavir and arbidol. Heparin shows benefit in patients with severe COVID-19 infections.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent No patients or test subjects were required in the formation of this meta-analysis.

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