Pharmacological treatment for patients with coronavirus disease 2019: systematic review of randomized controlled trials

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Systematic Review

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Background: The best treatment for COVID-19 is not known, with numerous agents under investigation. We determined the outcomes of patients with COVID-19 treated with different pharmacological agents.

Methods: In this systematic review, we searched Ovid MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials for studies published between 1st January and 12th August, 2020. We included randomized controlled trials (RCTs) of patients with COVID-19 treated with any pharmacological agent and compared with a different pharmacological agent, placebo or standard of care.

Results: From 6346 citations, 19 studies were included, with an overall low risk of bias. Two RCTs evaluated the use of remdesivir in laboratory-confirmed moderate-to-severe COVID-19. One study found that 10 days of remdesivir was associated with shortened recovery time. Neither found reduction in mortality. One RCT found no association of lopinavir/ritonavir with time to clinical improvement, or mortality benefit. Two RCTs of hydrochloroquine in patients with mild, early disease demonstrated no reduction in disease severity, hospitalization rate, death or viral load. Two RCTs observed no association of hydrochloroquine in hospitalized patients with mild-to-moderate disease with virological clearance, improvement in symptoms, need for respiratory support or death. One RCT showed that the use of steroids was associated with improved survival in patients with moderate-to-severe disease, especially those requiring respiratory support.

Conclusions: There is evidence for the benefit of steroids in patients with moderate-to-severe disease. Remdesivir might shorten recovery time in patients hospitalized with moderate-to-severe disease. There is currently no evidence to support the use of lopinavir/ritonavir or hydrochloroquine.

Study’s Registration: PROSPERO CRD42020184433.
Results

Overall, 6346 references were screened for eligibility. Of these, 39 full-text articles were assessed against inclusion and exclusion criteria. Nineteen articles met the inclusion criteria and were included in the systematic review and qualitative synthesis (Supplementary Figure 1). Thirteen out of 19 studies included patients with moderate-to-severe disease, and 16 studies enrolled hospitalized patients. Most of the studies were deemed to have low risk of bias (Supplementary Tables 1-3).

Two RCTs assessed the effect of remdesivir on hospitalized patients with laboratory-confirmed moderate-to-severe COVID-19. While a small study from China (n=237) did not find difference in time to clinical improvement between remdesivir and placebo during 28 days follow up, a larger multi-country study (n=1059) reported that 10 days of remdesivir was associated with shortened time to recovery (11 vs. 15 days) during 28 days follow up. Neither study found reduction in mortality at day 14 after enrollment (Table 1). ROB was low/unclear in some domains (Supplementary Table 1).

A study investigating lopinavir/ritonavir in patients with laboratory-confirmed COVID-19 did not meet the primary outcome of the study of time to clinical improvement, evaluated at day 28, and also did not show reduction in mortality (Table 1). ROB was low (Supplementary Table 1). Studies of combination regimens of lopinavir/ritonavir with other antivirals and other immunomodulators were also included. In patients receiving lopinavir/ritonavir combined with novaferon, compared with novaferon alone, the percentage of patients with negative SARS-CoV-2 PCR was higher at day 3 and 6 after randomization, and the median time until negative SARS-CoV-2 PCR was shorter (Table 1). In another study, the combination of lopinavir/ritonavir with IFN b-1b and ribavirin (RBV) was associated with shorter time until negative SARS-CoV-2 PCR, shorter time to resolution of symptoms and decreased hospital length of stay (LOS), compared with lopinavir/ritonavir alone. ROB was low in both studies (Supplementary Table 1).

Four RCTs investigated HCQ use in hospitalized and clinic patients. Two of these RCTs reported that early treatment of outpatients with mild disease (4-5 days after symptoms onset) did not reduce disease severity, hospitalization rate, death or SARS-CoV-2 viral load (Table 1). ROB was variable in these studies (Supplementary Table 1). Two other RCTs found no difference in virological clearance during 28 days follow up after HCQ administration in hospitalized patients with mild-to-moderate disease. HCQ administration was also not associated with difference in symptoms, need for respiratory support or death (Table 1). ROB was low for most domains in these two studies (Supplementary Table 1).

Two published RCTs that assessed the effect of administration of steroids on 28-day mortality were identified. The first was an interim analysis of the RECOVERY trial that found that administration of dexamethasone resulted in a lower case-fatality rate compared with standard of care. Subgroup analyses indicated that the finding was prominent among patients receiving invasive mechanical ventilation, but not observed in patients not receiving respiratory support at randomization. A study in Brazil with a lower number of patients randomized, reported that methylprednisolone did not result in a reduction in 7-day, 14-day or 28-day case-fatality rate compared with placebo (Table 2). The two studies had low ROB (Supplementary Table 2).

Four RCTs that evaluated immunomodulators (other than steroids) as single agents in treating COVID-19 patients were identified (Table 3). The rate of hospitalization was not different in outpatients treated with febuxostat compared with HCQ. Receipt of IFN b-1a did not result in improvement in time to clinical response, although mortality benefit was noted, especially if administered within 10 days of symptoms onset. In a small study, colchicine was associated with improved time to clinical deterioration. Ruxolitinib receipt did not result in reduction in time to clinical improvement or mortality benefit. Overall, the studies were found to have low ROB (Supplementary Table 3).

Discussion

There is an urgent need to establish the optimal pharmacological treatment of patients with COVID-19. In this systematic review, we aimed to assess the effect of different pharmacological treatments on outcomes in patients with COVID-19. Remdesivir was found to be associated with shortened time to clinical improvement in patients hospitalized with moderate-to-severe disease. In addition, an improved survival rate was noted for steroids administered to patients, especially those who required mechanical ventilation and/or supplemental oxygen at diagnosis. Lopinavir/ritonavir was not associated with clinical improvement and did not demonstrate mortality benefit. HCQ administered to outpatients or inpatients did not reduce the severity of disease or hospitalization rates, enhance virological clearance, improve symptoms, reduce need for respiratory support or prevent death.

Remdesivir is an inhibitor of the viral RNA polymerase and has been shown to have inhibitory activity against SARS-CoV-2, SARS-CoV-1 and MERS-CoV in vitro (8-12). While a small study did not find that remdesivir administration was associated with shortening of time to clinical improvement (13), a multi-country study found that a 10 days course of Remdesivir was associated with shortening of time to recovery (14). However, current evidence from both studies did not support that there is reduction in mortality at day 14 after randomization. It should be noted that the former study did not complete full enrollment (due to the end of outbreak in China) of the target number of patients, and thus had a lower sample size that might have precluded any definite conclusion. In addition, the modest clinical benefit observed (14) with a highly expensive drug might challenge its use in some settings (e.g. low-middle income countries). Experience
Lopinavir is a protease inhibitor, and is combined with ritonavir to increase lopinavir’s plasma half-life through the inhibition of cytochrome P450. This combination is an established agent in the treatment of HIV. Lopinavir has in vitro inhibitory activity against SARS-CoV-1 (17, 18), the causative agent of SARS disease. Lopinavir also has activity against MERS-CoV observed in vitro (19) and in an animal model (20). The addition of RBV to lopinavir/ritonavir reduced the risk of ARDS or death, as well SARS-CoV-1 viral load among patients with SARS (21). The combination of lopinavir/ritonavir, RBV and IFN α has been associated with survival in case reports of patients with MERS (22-24). In this systematic review, one RCT did not find lopinavir/ritonavir to be associated with shorter time to clinical improvement, or have mortality benefit in patients with SARS-CoV-2 (25). One RCT found that the combination of IFN b-1b, lopinavir/ritonavir, and RBV was associated with shorter time to negative SARS-CoV-2 PCR, shorter time to resolution of symptoms and decreased hospital LOS, compared with lopinavir/ritonavir alone (26). This might have practical implications related to isolation precautions for patients. In addition, reduction of hospital LOS might enable health service to cope with higher load of patients, provide better care in severe disease, and might also reduce costs of hospitalization.

Chloroquine and its hydroxyl analogue HCQ are well known as antimalarial drugs. Both drugs have been shown to block the viral replication of SARS-CoV-2 in cell cultures, suggesting that they might have potent antiviral activity against SARS-CoV-2 in vivo (12, 27). In our systematic review, two RCTs performed on outpatients found no reduced disease severity or hospitalization rates after treatment with HCQ early in the course of mild disease (28, 29). Two RCTs on the use of HCQ in hospitalized patients also failed to demonstrate that HCQ administration for patients with mild-moderate disease enhanced virological clearance, improved symptoms, reduced need for respiratory support or prevented death (30, 31).

One of two published studies showed that dexamethasone treatment was associated with reduction in 28-day mortality, especially among patients who required invasive mechanical ventilation or supplemental oxygen (32). While this finding was not supported by a recent study from Brazil, which also recruited patients with moderate to severe COVID-19, differences in the results might stem from the lower number of patients, the later presentation after symptoms onset and the higher baseline mortality rate without steroids in the latter compared with the former study (33). A recent prospective meta-analysis of RCTs that evaluated the efficacy of corticosteroids in critically ill patients found that corticosteroid administration was associated with a reduction in 28-day mortality when compared with SOC or placebo (odds ratio 0.66, 95% CI: 0.53-0.82) (34). Thus, The World Health Organization (WHO) is currently considering amending their COVID treatment guidelines to recommend the use of steroids in the treatment of critically ill patients. Limited data from earlier SARS outbreaks were not conclusive regarding the benefit of steroids (35). Systematic review of the use of corticosteroids in patients with MERS did not suggest a reduction in mortality, and was associated with delayed MERS-CoV RNA clearance (36).

Investigation of other immunomodulatory agents as a single agent has shown less promising results, and published articles were limited by small number of patients. Among the 4 articles identified, receipt of IFN-1a might have mortality benefit especially if administered early in the course of the disease (37). However, the high costs of these drugs might preclude their use, especially in low-middle income countries settings. IFN b was found to be the most potent inhibitor of SARS-CoV among other IFNs (38). However, a retrospective study showed that RBV plus recombinant IFN (rIFN-α2a, rIFN-α2b, or rIFN-β1a) did not result in a reduction in 90-day mortality amongst patients with severe MERS-CoV infection (38).

Conclusions

Remdesivir is associated with shortening time to clinical improvement in patients hospitalized with moderate-severe disease, and its use should be supported by future research. Currently, there is no evidence to support the use of HCQ in either outpatients with mild disease or inpatients with mild-moderate disease, nor the use of lopinavir/ritonavir in hospitalized patients. Our systematic review supports the use of steroids in critically ill patients.

There is a need to investigate the role of pharmacological treatment in adults with some underlying comorbidities (e.g. human immunodeficiency virus infection) or other specific populations (e.g. pediatric population, pregnant women) who have up to now largely been excluded from RCTs. In addition, there is a need to further explore the role of steroids in the treatment of moderate-severe COVID-19 as well as the optimal dose and duration of corticosteroid therapy in critically ill cases. Meta-analysis of effects of different pharmacological treatments may be possible as additional RCTs are published.

List Of Abbreviations

COVID-19: Coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ARDS: acute respiratory disease syndrome
 ICU: intensive care unit

 HCQ: hydrochloroquine

 RCTs: randomized controlled trials

 SOC: standard of care

 ROB: Risk of bias

 RBV: ribavirin

 LOS: length of stay

 Declarations

 Ethics approval and consent to participate: Not applicable.

 Consent for publication: Not applicable.

 Availability of data and material: Not applicable.

 Competing interests: BA, VK, HM, AC, RL, CP, RC declare no competing interests. MS has been an investigator on projects funded by GlaxoSmithKline, Merck, Pfizer, Sanofi-Pasteur, Seqirus, Symvivo and VBI Vaccines. All funds have been paid to his institute, and he has not received any personal payments.

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 Authors' contributions: All authors conceived and designed the systematic review. BA, VK, HM, AC, RL, CP, RC searched the scientific literature. BA, HM, AC, RL, CP, RC, RD drafted the tables. BA wrote the first draft of the manuscript. All authors critically reviewed and edited the manuscript. All authors reviewed and approved the final version of the manuscript.

 Acknowledgements: Not applicable.

 Tables

 Table 1: Summary of findings table of randomized controlled trials of anti-infective agents for treatment of COVID-19
<table>
<thead>
<tr>
<th>Study settings</th>
<th>Cohort characteristics</th>
<th>Treatment</th>
<th>Months</th>
</tr>
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<tbody>
<tr>
<td><strong>Lop-Rit</strong></td>
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<tr>
<td><strong>Lop-Rit vs. SOC</strong></td>
<td>Jin Yin-Tan Hospital, Wuhan, China (18-Jan-2020 – 03 Feb 2020)</td>
<td>Laboratory-confirmed by SARS-CoV-2 RT-PCR of respiratory tract samples, pneumonia confirmed by radiology</td>
<td>Moderate-severe</td>
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<td><strong>Rem</strong></td>
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<td><strong>Rem vs Pla</strong></td>
<td>Ten hospitals in Hubei Province, China (06-Feb-2020-12-Mar 2020)</td>
<td>Laboratory-confirmed by SARS-CoV-2 RT-PCR and pneumonia confirmed by radiology</td>
<td>Moderate-severe</td>
</tr>
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</table>
### Rem vs. Pla

<table>
<thead>
<tr>
<th>Multi-country****, (21-Feb-2020 to 19-April-2020)</th>
<th>Laboratory-confirmed COVID-19</th>
<th>Moderate - Severe</th>
<th>Mean 58.9 [SD:15]</th>
<th>M: 684/1063 (64.3%)</th>
<th>HTN: 460/928 (49.6%)</th>
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<tr>
<td>CHD: 17/237 (7.1%)</td>
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<td>Group 2: Pla, 79 patients (allowed steroids)</td>
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### HCQ

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<tr>
<td>Multi-center, 3 province in China (11 to 29)</td>
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<td>HCQ plus SOC vs. SOC</td>
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<tr>
<td>Multi-center, 3 province in China (11 to 29)</td>
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<td>Group 1: HCQ 1200 mg daily for 3 days followed by</td>
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### Pe

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| HCQ vs. SOC | Suspected or laboratory confirmed COVID-19 by SARS-CoV-2 RT-PCR | Mild to moderate hospitalized | Mean: 50.3 (SD: 14.6) | M: 388/665 (58.3%) | HTN: 258/665 (38.8%) | Median: 7 (IQR: 5-9) | Group 1: HCQ: 400mg dose 2x daily (7 days), 221 patients | Multicenter, Brazil, (29 Mar 20 – 02 Jun 20) | Suspected or laboratory confirmed COVID-19 by SARS-CoV-2 RT-PCR | HCQ and AZM vs. SOC | - Prneg coin SA 28 bet an 85 CI vs. CI res 75 patients | 800 mg daily (2 weeks for mild-moderate disease and 3 weeks for severe disease), 75 patients. | Group 2: SOC, 75 patients | - M neg coin sin HC vs. 0.8 0.5 Ott | - Pr neg coin 7. da the | - P all sir 28 sin vs. vs. |
### Outpatient

#### HCQ vs. Pla

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<th>Multi-site, United States and Canada (22-March-2020 to 20-May-2020)</th>
<th>Laboratory-confirmed by SARS-CoV-2 RT-PCR or COVID-19-compatible symptoms with epidemiologic link</th>
<th>Mild outpatient (4 or fewer days of symptoms)</th>
<th>Median 40 [IQR: 32-50]</th>
<th>M: 185/423 (44%)</th>
<th>Asthma: 48/423 (11%), HTN: 46/423, 11%, DM: 15/423 (4%), 236/423 (56%) of participants enrolled within 1 day of symptom onset</th>
<th>Group 1: HCQ 800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 more days, 212 patients</th>
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#### HQC vs. SOC

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<tr>
<th>Multi-site, Spain (17-March-2020 to 26-May-2020)</th>
<th>Laboratory-confirmed by SARS-CoV-2 RT-PCR</th>
<th>Mild outpatient (e.g. &lt;5 days of symptoms)</th>
<th>Mean 41.6 (SD: 12.6)</th>
<th>M: 31.4% 92/293</th>
<th>CVD: 35/293 (11.9%), RD: 17/293 (5.8%), neurological disease: 40/293 (13.7%), Median 3 [IQR: 2-4]</th>
<th>Group 1: HCQ 800 mg on day 1, followed by 400 mg once daily for 6 days, 136 patients</th>
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Other treatments

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<tr>
<th>Treatment</th>
<th>Study Details</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>RBV + IFNa vs. Lop.Rit + IFNa vs. RBV + LPV/Rit + IFNa</td>
<td>Chongqing Public Health Medical Center, China (20 Jan 2020 – 25 Feb 2020)</td>
<td>Laboratory confirmed by SARS-CoV-2 RT-PCR, Mild to moderate</td>
</tr>
</tbody>
</table>
|                 | Mean: (SD: 11.5) M: 46/101 (46%) Median 4.0 (IQR 1.5 – 7.0)                | Group 1: RBV: IV 2 g loading dose, oral doses 400-600mg/8 hour, IFNa inhaled 5 million U or 50mg/dose 2x daily (14 days), 33 patients
|                 |                                                                           | Group 2: Lop.Rit: oral 400mg/100mg per dose 2x daily (14 days), IFNa inhalation 5 million U or 50mg/dose 2x daily (14 days), 36 patients
|                 |                                                                           | Group 3: RBV: IV 2 g loading dose, oral doses 400-600mg/8 hours, Lop.Rit: oral dose 400mg/100mg per dose 2x daily (14 days), IFNa inhalation 5 million U or 50mg/dose 2x daily (14 days), 32 patients
|                 |                                                                           | Pe Pri out N dif fro init SA nu reg me da;                               |
| IFN beta-1b, Lop-Rit and RBV vs Lop-Rit | Six hospitals in Hong Kong, (10-Feb and 20-Mar 2020) | Laboratory confirmed COVID-19 t, Mild-moderate Median: 52 (IQR: 32–62) M: 68/127 (54%) DM: 17/127 (13.4%), HTN: 36/127 (28.3%), CHD: Median 5 (IQR 4–7) in the combination group and 4 (IQR 3–8) in the control group Group 1: Lop 400 mg and Rit 100 mg every 12 h, RBV 400 mg every 12 h, and 1-3 doses of IFN beta-1b on Pe Pri out T }
**Favipiravir vs. SOC**

Six hospitals, Russia, Apr-May 2020

Laboratory confirmed COVID-19 pneumonia

Moderate

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<tr>
<th>Favipiravir</th>
<th>SOC: mean 48.6 (16.1)</th>
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<tr>
<td>1600/600 mg: mean 51.0 (15.6)</td>
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<td>1800/800 mg: mean 52.6 (15)</td>
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Favipiravir 1600/600 mg: mean 51.0 (15.6)

Favipiravir 1800/800 mg: mean 52.6 (15)

M 30/60 (50%)

≥ 60 years and/or chronic diseases:

28/60 (46.7%)

N/A

Group 1: Favipiravir 1600 mg BID day 1, 600 mg BID days 2-14, 20 patients

Group 2: Favipiravir 1800 mg BID day 1, 800 mg BID days 2-14, 20 patients (10% received steroids)

Group 3: SOC, 20 patients (75% received HCQ or CQ, 5% Lop/Rit, 10% steroids

Group 2: Lop 400 mg and Rit 100 mg every 12 h for 14 days, 41 patients

Group 1: Lop 200 mg and Rit 100 mg every 12 h for 14 days, 40 patients

SOC: mean 48.6 (16.1)

N/A
### Nova vs. Nova plus
#### Lop/Rit vs. Lop/Rit

| Nova: | Median 46.5 Days (IQR: 40-63.8); Nova with Lop/Rit 50: (37.8-62.8); Lop/Rit :37 (26-54) | M: 42/89 (47.1%) | DM: 8/98 (9%) | Nova: Median 4 (IQR: 3-6.5); Nova with Lop/Rit 7.0 (3.3-11.3); Lop/Rit 4 days (3-6) in Group 1: Inhaled Nova 20 μg BID alone, 30 patients
Group 2: Inhaled Nova 20 μg BID with Lop/Rit, 2 tablets BID, 30 patients
Group 3: Lop/Rit, 2 tablets BID, 29 patients |
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<td>Moderate-severe</td>
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### Leflunomide vs. SOC

<table>
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<tr>
<th>Leflunomide vs. SOC</th>
<th>Single Hospital, China 20-Feb-2020 to 28-Feb-2020</th>
<th>Moderate</th>
<th>Mean 54.9 [SD: 6.14]</th>
<th>M: 3/10 (30%)</th>
<th>HTN: 6/10 (60%), Hyperlipidemia: 1/10 (10%), atherosclerosis: 3/10 (30%), COPD: 1/10 (10%)</th>
<th>Mean 9.2 [SD: 0.8]</th>
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</table>
| Laboratory confirmed using qRT-PCR for SARS-CoV-2 | | | | | Group 1: Oral Leflunomide (10 mg per tablet), 50 mg every 12 h, three consecutive times, after 20 mg every day – a total course of 10 days, 5 patients
Group 2: Blank control without a placebo, but with SOC, 5 patients |

### DRV/Cob

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<tr>
<th>DRV/Cob</th>
<th>Shanghai</th>
<th>Moderate to</th>
<th>Mean:</th>
<th>M: Cardio</th>
<th>Median: 4</th>
<th>Group 1: Pe</th>
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<tr>
<td>vs. SOC</td>
<td>Public Health Clinical Center, China 30 Jan 2020 – 06 Feb 2020</td>
<td>confirmed using SARS-CoV-2 RT-PCT</td>
<td>Severe.</td>
<td>47.2 (SD: 2.8)</td>
<td>18/30 (60%)</td>
<td>Vascular disease: 8/30 (26.7%)</td>
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<td>DM:</td>
<td>2/30 (6.7%)</td>
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<tr>
<td>Group 2:</td>
<td>SOC, no oral antiviral drugs, 15 Patients</td>
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<td>All received IFNa-2b + SOC per guidelines from China</td>
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**Abbreviations:** Ref: reference; Lop-Rit: Lopinavir-ritonavir; RT-PCR: reverse-transcriptase–polymerase- chain-reaction; NA: not available; SOC: standard of care; IQR: interquartile range; M: male; DM: Diabetes mellitus; ITT: intention to treat; LOS: length of stay; O2: oxygen; HTN: Hypertension; CHD: Coronary Heart Disease; Rem: Remdesivir; Pla: placebo; CQ: Chloroquine Diphosphate; CKD: Chronic kidney disease; OR: Odds ratio; IFN: interferon; SOFA: Sequential organ failure assessment; Nova: Novaferon; CVD: Cerebrovascular disease; IMV: invasive mechanical ventilation; N/A: not available; HR: Hazard ratio; HD: Heart Disease; CVD: cardio vascular disease; RD: respiratory disease; AZM: Azithromycin; OB: obesity; RBV: Ribavirin, LPV: Lopinavir, URT: Upper respiratory tract; COPD: Chronic obstructive pulmonary disease; DRV/c: Darunavir/cobicistat, URT: upper respiratory tract; Cob: Cobicistat. * Number out of total and % ** Study terminated early and thus clinical outcomes not presented *** Use of glucocorticoids, immunomodulators, antivirals, antibiotics allowed for all groups; **** Countries included: US, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore.

**Table 2:** Summary of findings table of randomized controlled trials of steroid treatment for COVID-19
<table>
<thead>
<tr>
<th>Study settings</th>
<th>Cohort characteristics</th>
<th>Treatment</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamethasone vs. SOC</strong></td>
<td></td>
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<td><strong>Per ITT:</strong></td>
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<tr>
<td>176 centers, UK (19-Mar to 8-June-2020)</td>
<td>Clinically suspected or laboratory-confirmed SARS-CoV-2 infection**</td>
<td></td>
<td><strong>Primary outcomes:</strong></td>
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</table>
| | Mean (SD): 66.1 (15.7) | Dexamethasone: median 8 (IQR: 5-13); SOC: median 9 (IQR: 5-13) | - Mortality at days significantly lower in the dexamethasone SOC, 22.9% vs. 25.7%.
| | M: 4087/6425 (63.6%) | | - Mortality at days significantly lower in the dexamethasone SOC among patients receiving IMV, 29.3% vs. 41.4%.
| | DM: 1546/6425 (24%), CHD: 1757/6425 (27.3%) | | - Mortality at days significantly lower in the dexamethasone SOC among patients receiving oxygen with, 23.3% vs. 26%
| | Time between onset of symptoms and randomization in days | | - Mortality at days not significantly different in the dexamethasone SOC among patients who were not receiving respiratory support at randomization, 17.8% vs. 14%
| | | | Other outcomes:
| | | | - Hospital LOS significantly lower in the dexamethasone SOC (me vs. 13 days) |
| | | | - Probability of discharge within 28 days higher in dexamethasone SOC (rate ratio 95% CI: 1.03-1.27) with greatest among patients receiving IMV randomization |
| | | | - Risk of progression to IMV lower in dexamethasone SOC (risk ratio 95% CI: 0.62-1.03)
| **MP vs Pla** | | | **Per modified:** |
| Hospital Pronto-Socorro Delphina Rinaldi Abdel Aziz, Brazil (18-Apr-2020 – 16-June-2020) | Hospitalized patients with clinical and/or radiological suspicion of COVID-19*** | | **Primary outcomes:** |
| | Mean (SD): 55 (15) | M: 254/644 (64.6%) | - 28-day mortality not different vs Pla, 37.1% vs. 38.1% (HR: 0.95% CI: 0.66-1.27).
| | DM: 106/364 (29.1%) | Median: 13 days (IQR: 9-16) | Other outcomes:
| | HTN: 178/364: (48.9%) | | - Hospital LOS significantly lower in MP vs. Pla (me vs. 13 days)
| | Alcohol use disorder: 96/363 (27%) | | - Probability of discharge within 28 days higher in MP (rate ratio 95% CI: 1.03-1.27)
| | | | - Risk of progression to IMV lower in MP (rate ratio 95% CI: 0.62-1.03)
- 7-day and mortality not different in M Pla.
- Presence of RNA in naso/oropharyngeal swab on day 7 not different MP vs Pla.
- Need for IV on day 7 or Hos LOS not different MP vs. Pla.
- Reduced 28-day mortality in M group in post analysis including patients >60.

Abbreviation: COVID-19: Coronavirus disease 19; Ref: reference; SD: Standard deviation; IQR: interquartile range; NA: not available; SOC: standard of care; M: male; DM: Diabetes mellitus; ITT: intention to treat; LOS: length of stay; O2: oxygen; HTN: Hypertension; CHD: Coronary Heart Disease; Pla: placebo; MP: Methylprednisolone; IV: Intravenous; IMV: invasive mechanical ventilation.

* Number out of total and %; ** 88% confirmed in dexamethasone and 89% in SOC group; *** 83% of MP and 79% of Pla were laboratory confirmed by SARS-CoV-2 RT-PCR.

Table 3: Summary of findings table of randomized controlled trials of immunomodulatory treatment for COVID-19.
<table>
<thead>
<tr>
<th>Study settings</th>
<th>Cohort characteristics</th>
<th>Treatment</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBX vs. HCQ</strong></td>
<td>Mostafavian Fever Clinic in Sari, Iran (16-Mar-2020 to 10-Apr-2020)</td>
<td>Clinical and radiological suspicion of COVID-19, or clinical suspicion and epidemiological link to COVID-19 case</td>
<td><strong>Per protocol</strong> Primary outcome - Rate of hospitalization not different between groups. <strong>Other outcome</strong> - Mean percentage lung involvement by chest X-ray reduced from 16 to 7.3 FBX and to 8% in group at 14 days.</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>Mean: Age in years M: Sex Main comorbidities* Time between onset of symptoms and randomization in days Drugs: Agent, dosage, duration, number of patients</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Clinically defined cases</td>
<td>Mean: 57.5 M: 32/54 (59.3%) DM: 15/54 (27.8%)</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Mean: Age in years M: Sex Main comorbidities* Time between onset of symptoms and randomization in days Drugs: Agent, dosage, duration, number of patients</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Mean: Age in years M: Sex Main comorbidities* Time between onset of symptoms and randomization in days Drugs: Agent, dosage, duration, number of patients</td>
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<td></td>
<td>Severe</td>
<td>Mean: Age in years M: Sex Main comorbidities* Time between onset of symptoms and randomization in days Drugs: Agent, dosage, duration, number of patients</td>
<td>N/A</td>
</tr>
<tr>
<td>IFN b-1a vs. SOC</td>
<td>Imam Khomeini Hospital Complex, Iran (29 Feb 2020 – 3 Apr 2020)</td>
<td>Laboratory confirmed by SARS-CoV-2 RT-PCR, or clinical and radiological suspicion of COVID-19</td>
<td><strong>Per protocol</strong> Primary Outcome - Time to clinical response significa different between IFN b-1a and the control groups (1:8.3 days). <strong>Other outcome</strong> - Administered IFN b-1a before 1% of symptomatic onsets significa reduced mortality (OR=13.8 CI=1.5-111 while late administrtation did not s significa effects (OR=2.1 CI=0.489) Hospital ICU LOS duration mechani...</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>Mean: Age in years M: Sex Main comorbidities* Time between onset of symptoms and randomization in days Drugs: Agent, dosage, duration, number of patients</td>
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</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Patient Characteristics</td>
<td>Treatment</td>
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</tbody>
</table>
| **Colchicine vs. SOC** | 16 tertiary care hospitals, Greece (03-April-2020 – 27 April 2020) | Laboratory-confirmed by SARS-CoV-2 RT-PCR | Moderate-severe | Group 1: Colchicine (1.5 mg loading dose followed by 0.5 mg and maintenance of 0.5 mg twice daily) for 3 weeks or until hospital discharge, 55 patients  
Group 2: SOC **, 50 patients. | Per ITT  
Primary outcome  
- Deterioration by 2 points on a 7-grade scale, with weeks or discharge higher in SOC vs. Colchicine group (14.1.8%) (OR=0.11 CI: 0.01-0.096). |
| **Ruxolitinib vs. Pla** | Three hospitals, China (9-Feb-2020 – 28-Feb-2020) | Clinically suspected, epidemiologically linked or laboratory confirmed cases | Severe | Group 1: Ruxolitinib 5 mg twice a day with SOC, 20 patients  
Group 2: Placebo (100 mg Vitamin C) twice a day with SOC, 21 patients | Modified  
Primary outcome  
- No significance difference in hospital between Ruxolitinib SOC and Pla (median 12 vs. 13 days).  
| **Other outcomes** | | | | |
- 28-day mortality statistics different Ruxolitin Pla (0% \( v \) 14.3%)
- Time from randomisation to discharge not statistically different (median 16 days)
- Median time to virus clearance statistically significant Ruxolitin Pla (median 13 vs. 12 days) (H ratio, 0.7 (95% CI: 0.2257).

Abbreviations: COVID19: Coronavirus disease 2019; Ref: reference; FBX: Febuxostat; HCQ: Hydrochloroquine; SOC: Standard of care; SC subcutaneous; SD: standard deviation; IQR: interquartile range; N/A: not available; ITT: Intention to treat; M: male; DM: Diabetes Mellitus; HTN: Hypertension, CHD: Coronary heart disease; OR: odds ratio; ICU: intensive care unit; CAD: Coronary artery disease. * Number out of total and % ** Chloroquine or hydroxychloroquine, azithromycin, lopinavir or ritonavir, tocilizumab.

References


