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

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Systematic Review

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Abstract

**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.

Background

Coronavirus disease 2019 (COVID-19) is a rapidly spreading and fatal pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Disease symptoms can range from mild-to-moderate influenza-like symptoms to severe acute respiratory disease syndrome (ARDS) necessitating admission to the intensive care unit (ICU) for ventilator and hemodynamic support, and leading to fatalities which are more prevalent in adults and older individuals with comorbidities (1-3). While mild-to-moderate COVID-19 is a self-resolving disease, pharmacological treatment might be indicated in more severe cases, and includes drugs that target either key steps of the virus life cycle or the host immune response to SARS-CoV-2. Given the current lack of evidence to support the use of most drugs, the use of COVID-19 pharmacological therapies is recommended mainly in the setting of clinical trials (4).

An observational study did not demonstrate benefit of lopinavir/ritonavir (1). Some other antiviral (remdesivir (5)) and immunomodulatory agents (e.g. hydrochloroquine [HCQ] and azithromycin(6)) have shown favorable results in non-randomized studies. However, these studies should be interpreted carefully due to limitations in study design. We aimed to review the outcomes of patients with COVID-19 treated with different pharmacological treatments in randomized controlled trials (RCTs).

Methods

**Search strategy and selection criteria**

In this systematic review, we used a methodologically rigorous approach (Cochrane Handbook of Systematic Reviews) including stringent formulation of the research question and development of the protocol; double-blind screening and selection of the literature; data extraction; and collation, and report of the results. We developed a search strategy and refined its parameters in consultation with a research librarian (member of our research team). We searched Ovid MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials databases for published studies in English exploring the benefit of different pharmacological agents on outcome in patients with COVID-19, published between 1st January and 12th August, 2020 following PRISMA guidelines (7) (Ovid MEDLINE search criteria in Supplementary method). We included randomized studies of patients with COVID-19 treated with a specific pharmacological agent and a control group treated with a different pharmacological agent, placebo or standard of care (SOC) only, in which outcomes (clinical, radiological, and/or virological) were reported. We excluded studies that did not contain a control group, non-human studies, non-randomized studies, cluster-randomized studies and studies in which no outcomes were reported. Letters, editorials and review articles containing no primary data were excluded. Inclusion and exclusion criteria were specified in advance and documented in the study protocol. References were screened by title and abstract by two authors, with disagreements resolved in a group discussion. Articles screened and found to be possibly eligible were fully assessed against inclusion and exclusion criteria by two authors, with controversies resolved by group discussion.

**Data extraction**

Data were extracted from articles that met the inclusion criteria independently by two authors and included the following: study settings, cohort characteristics, treatments investigated and main results. Disagreements between authors were resolved by discussion including a third author.

**Risk of bias assessment**

Risk of bias (ROB) of included RCTs was assessed against the Cochrane ROB tool for RCTs. The study was registered at PROSPERO International prospective register of systematic reviews (CRD42020184433).

**Role of the funding source**: There was no specific funding source for this study.
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-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 ß-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-ß1a) 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: hydroxychloroquine

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.

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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 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.

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Tables

Table 1: Summary of findings table of randomized controlled trials of anti-infective agents for treatment of COVID-19
| Study settings          | Cohort characteristics                                                                 | Treatment                                                                 | Ms |
|-------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------|----|
|                         | Case definition                                                                        | Severity                                                                 |     |
|                         | Cohort characteristics                                                                 | Age in years                                                             | Sex* |
|                         | Treatment                                                                               | Main comorbidities*                                                      | Time between onset of symptoms and randomization, in days |
|                         | Drugs: Agent, dosage, duration, number of patients                                       |                                                                          |     |
| **Lop-Rit**             | Laboratory-confirmed by SARS-CoV-2 RT-PCR of in respiratory tract samples, pneumonia confirmed by radiology | Moderate-severe                                                          |     |
| Lop-Rit vs. SOC         | Jin Yin-Tan Hospital, Wuhan, China (18-Jan-2020 – 03 Feb 2020)                         | Median:58 (IQR: 49-68)                                                  | M: 120/199 (60.3%) |
|                         |                                                                                         | DM: 23/199 (11.6%),                                                      | Median: 13, (IQR:11-16) |
|                         |                                                                                         | CVD: 13/199 (6.5%),                                                      | Group 1: Lop-Rit: 400mg and 100mg twice daily for 14 days, 99 patients |
|                         |                                                                                         | Cancer: 6/199 (3%)                                                      | Group 2: SOC, 100 patients |
|                         |                                                                                         |                                                                          |     |
| **Rem**                 | Laboratory-confirmed by SARS-CoV-2 RT-PCR of in respiratory tract samples, pneumonia confirmed by radiology | Moderate-severe                                                          |     |
| Rem vs Pla              | Ten hospitals in Hubei Province, China (06-Feb-2020-12-Mar 2020)                        | Median 65 years (IQR: 56–71)                                            | M: 140/237 |
|                         |                                                                                         | HTN: 167/237 (70.4%)                                                   | Median 10-11 days |
|                         |                                                                                         | DM: 56/237 (23.6%)                                                    | Group 1: Rem 200 mg on day 1, 100 mg on days 2–10 in single daily infusions, 158 patients |
|                         |                                                                                         |                                                                          |     |

**Note:**
- Significant difference (sig) is denoted.
- Similarity (sh) indicates a lack of significant difference.
- Patients with laboratory-confirmed SARS-CoV-2 RT-PCR, pneumonia confirmed by radiology.
| Rem vs. Pla | Multi-country****, (21-Feb-2020 to 19-April-2020) |
| --- | --- |
| CHD: | 17/237 (7.1%) |
| Group 2: Pla, 79 patients (allowed steroids) |
| HR Proc | 0.8 |
| Group 2: Pla, 79 patients (allowed steroids) |
| 21 st | 0.8 |
| CHD: | 17/237 (7.1%) |

**Laboratory-confirmed COVID-19**

**Mild - Severe**

Mean 58.9 [SD:15] M: 684/1063 (64.3%)

HTN: 460/928 (49.6%)

Obesity: 342/925 (37%)

DM: 275/927 (29.7%)

Median: 9 [IQR:6 -12].

**Group 1:**

Rem: 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days, 538 patients

**Group 2:**

Saline placebo, up to 10 days, 521 patients

**Hospitalized HCQ**

**Hospitalized HCQ plus SOC vs. SOC**

**Multi-center, 3 province in China (11 to 29)**

**Laboratory confirmed COVID-19 by SARS-COV-2 RT-PCR**

**Mild-Moderate disease hospitalized (1% had severe disease)**

Mean: 46 (SD:14.7) M: 82/150 (55%)

DM: 21/150 (14%)

Mean: 16.6 (SD 10.5)

Group 1: HCQ 1200 mg daily for 3 days followed by

**Pe**

(21-Feb-2020 to 19-April-2020)
| Group 1: HCQ | HCQ: 400mg dose 2x daily (7 days), 221 patients |
|--------------|-----------------------------------------------|
| HCQ vs. HCQ and AZM vs. SOC | Multicenter, Brazil (29 Mar 20 – 02 Jun 20) |
| Suspected or laboratory confirmed COVID-19 by SARS-CoV-2 RT-PCR | Mild to moderate hospitalized |
| Mean: 50.3 (SD: 14.6) | HTN: 258/665 (38.8%) |
| M: 388/665 (58.3%) | Median: 7 (IQR: 5-9) |
| DM: 127/665 (19.1%) |
| OB: 37/665 (16.3%) |
| Group 2: HCQ: 400mg dose 2x daily (7 days) and AZM 500mg dose 1x daily (7 days), 217 patients |
| Group 3: SOC, 227 patients |

800 mg daily (Pr neg con SA 28 bet an 85 CI: vs. CI vs.
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M: 388/665 (58.3%)
HTN: 258/665 (38.8%)
Median: 7 (IQR: 5-9)
### Outpatient

| **HCQ vs. Pla** | **Multi-site, United States and Canada** | **Laboratory-confirmed by SARS-CoV-2 RT-PCR or COVID-19-compatible symptoms with epidemiologic link** | **Mild outpatients (4 or fewer days of symptoms)** | **Median 40 [IQR: 32-50]** | **M:** 185/423 (44%) | **Asthma:** 48/423 (11%), HTN: 46/423 (11%), DM: 15/423 (4%), 236/423 (56%) of participants enrolled within 1 day of symptom onset | **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

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

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### Notes

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Other treatments

| Treatment                  | Location                          | Lab confirmation | Mild to moderate | Mean: | M:       | N/A | Median 4.0 (IQR:1.5-7.0) | Group 1: |
|----------------------------|-----------------------------------|------------------|------------------|-------|----------|-----|-------------------------|---------|
| RBV + IFNα vs. Lop.Rit + IFNα vs. RBV + LPV/Rit + IFNα | Chongqing Public Health Medical Center, China (20 Jan 2020 – 25 Feb 2020) | Laboratory confirmed by SARS-CoV-2 RT-PCR | Mild to moderate | 42.5 (SD:11.5) | 46/101 (46%) | N/A |  |

Chongqing Public Health Medical Center, China (20 Jan 2020 – 25 Feb 2020)

Laboratory confirmed by SARS-CoV-2 RT-PCR

Mild to moderate

Mean: 42.5 (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 inhalation 5 million U or 50mg/dose 2 x 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 2 x 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), 32 patients

IFNa: inhalation 5 million U or 50mg/dose 2 x daily (14 days), 32 patients

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 Rit100 mg every 12 h, RBV 400 mg every 12 h, and 1-3 doses of IFN beta-1b on
**Favipiravir vs. SOC**

Six hospitals, Russia, Apr-May 2020

Laboratory confirmed COVID-19 pneumonia

Moderate

Favipiravir 1600/600 mg: mean 51.0 (15.6)

M 30/60 (50%)

≥ 60 years and/or chronic diseases:

SOC: mean 48.6 (16.1)

M 30/60 (50%)

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

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Ch
Nova vs. Nova plus Lop/Rit vs. Lop/Rit
Single Hospital, China 1-Feb-2020 to 20-Feb 2020
Laboratory confirmed COVID-19
Moderate-severe
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%)
HTN: 6/89 (6.7%)
CHD 3/89 (3.4%)

Nova: Median 4 (IQR: 3.6-5.6);
Nova with Lop/Rit 7.0 (3.1-11.3);
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

Leunomide vs. SOC
Single Hospital, China
20-Feb-2020 to 28-Feb-2020
Laboratory confirmed using qRT-PCR for SARS-CoV-2
Moderate
Mean 54.9 [SD: 6.14]
M: 3/10 (30%)
HTN: 6/10 (60%), Hyperlipidemia: 1/10 (10%),
Atherosclerosis: 3/10 (30%), COPD: 1/10 (10%)
Mean 9.2 [SD: 0.8]

Group 1: Oral Leunomide (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 Shanghai Laboratory Moderate to Severe
Mean: M: Cardio Median: 4 Group 1:
### vs. SOC

| Public Health Clinical Center, China, 30 Jan 2020 – 06 Feb 2020 | confirmed using SARS-CoV-2 RT-PCT | Severe. | 47.2 (SD: 2.8) | 18/30 (60%) | Vascular disease: 8/30 (26.7%) | (IQR: 2-5) | DRV/Cob: 1 pill (800mg DRV, 150mg Cob) 1x daily (5 days), | PriOu |
|---------------------------------------------------------------|-----------------------------------|---------|----------------|-------------|-------------------------------|------------|------------------------------------------------|-------|
| Risk factors: DM: 2/30 (6.7%) | Vascular disease: 8/30 (26.7%) | | | | | | | |
| Group 2: SOC, no oral antiviral drugs, 15 Patients | | | | | | | | |
| All received IFNa-2b + SOC per guidelines from China | | | | | | | | |

#### 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
| Study settings | Cohort characteristics | Treatment | Main results |
|---------------|------------------------|-----------|--------------|
| **Dexamethasone vs. SOC** | Clinically suspected or laboratory-confirmed SARS-CoV-2 infection** | Time between onset of symptoms and randomization in days | Per ITT: |
| 176 centers, UK (19-Mar to 8-June-2020) | Moderate-critical | 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%. |
| | Mean (SD): 66.1 (15.7) | | - Mortality at days significantly lower in the dexamethasone SOC among patients receiving IMV, 29.3% vs. 41.4%. |
| | M: 4087/6425 (63.6%) | | - Mortality at days not significantly different in dexamethasone SOC among patients receiving oxygen with 23.3% vs. 26. |
| | DM: 1546/6425 (24%), CHD: 1757/6425 (27.3) | | - Mortality at days not significantly different in dexamethasone SOC among patients who not receiving respiratory support at randomization, 17.8% vs. 14. |
| | | | **Other outcome** |
| | | | - Hospital LOS significantly lower in dexamethasone SOC (me vs. 13 days) |
| | | | - Probability discharge alive within 28 days higher in dexamethasone SOC (rate ratio 95% CI 1.03-1.275) with greatest among patients receiving IMV randomization |
| | | | - Risk of progressing to IMV lower in dexamethasone SOC (risk ratio 95% CI 0.62-0.79) |

| MP vs Pla | Hospitalized patients with clinical and/or radiological suspicion of COVID-19*** | Moderate-severe | Per modified Primary outcome |
| Hospitalized patients with clinical and/or radiological suspicion of COVID-19*** | Mean (SD): 55 (15) | M: 254/646 (64.6%) | - 28-day mortality not different vs Pla, 37.1% vs. 38.1% (HR: 0.95% CI 0.66-1.275) |
| Pronto Socorro Delphina Rinaldi Abdel Aziz, Brazil (18-Apr-2020 – 16-June-2020) | DM: 106/364 (29.1%) | HTN: 178/364 (48.9%) | Other outcome |
| | Alcohol use disorder: 98/363 (27%) | | - Hospital LOS significantly lower in MP vs SOC (me vs. 13 days) |
| | Median: 13 days (IQR: 9-16) | | - Probability discharge alive within 28 days higher in MP vs Pla (rate ratio 95% CI 1.03-1.275) with greatest among patients receiving IMV randomization |
| | Group 1: IV/sodium succinate MP 0.5 mg/kg, twice daily for 5 days; 194 patients | | - Risk of progressing to IMV lower in MP vs Pla (risk ratio 95% CI 0.62-0.79) |
- 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 day 7 or Hos LOS not different MP vs Pla.
- Reduced 28 mortality in M group in post hoc analysis incl 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
| Study settings | Cohort characteristics | Treatment | Main res |
|----------------|------------------------|-----------|----------|
|                |                        | Time between onset of symptoms and randomization in days | Drugs: Agent, dosage, duration, number of patients |
|                |                        | N/A       | Group 1: FBX – 80 mg PO per day x 5 days, 29 patients |
|                |                        | Group 2: HCQ – 200 mg PO twice daily X 5 days, 25 patients |
|                |                        | Per protc | Primary outcome |
|                |                        | - Rate of hospitalization not different between groups. |
|                |                        | - Symptom improver at day 5 statistically significant from baseline in both groups. |
|                |                        | - Mean percent improvement in lung involvement by chest X-ray reduced from 16 to 7.3% in FBX and to 8% in group at 14. |

**FBX vs. HCQ**

Mostafavian Fever Clinic in Sari, Iran (16-Mar-2020 to 10-Apr-2020)

| Clinical and radiological suspicion of COVID-19, or clinical suspicion and epidemiological link to COVID-19 case |
|---------------------------------------------------------------|
| Moderate severity |
| Mean: M: 57.5 (SD: 1.26); Age in years: M: 32/54 (59.3%) |
| DM: 15/54 (27.8%); Main comorbidities: Lung Disease: 1/54 (1.9%) |
| Group 1: FBX – 80 mg PO per day x 5 days, 29 patients |
| Group 2: HCQ – 200 mg PO twice daily X 5 days, 25 patients |

**IFN b-1a vs. SOC**

Imam Khomeini Hospital Complex, Iran (29 Feb 2020 – 3 Apr 2020)

| Laboratory confirmed by SARS-CoV-2 RT-PCR, or clinical and radiological suspicion of COVID-19 |
| Severe |
| Mean: M: 56.50 (SD: N/A); Age in years: M: 44/81 (54.3%) |
| HTN: 31/81 (38.3%); DM: 22/81 (27.2%); CHD: 23/81 (28.4%); Main comorbidities: SOC: 61.00 (SD: N/A) |
| Group 1: 44 μg / ml (12 million IU/ml) IFN b-1a SC 3x weekly for 2 consecutive weeks, plus SOC (corticosteroids 61.9%), 42 patients |
| Group 2: SOC – HCQ (400 mg BD 1st day, then 200 mg with Lopinavir/Ritonavir (400/100 mg BD) or Atazanavir/Rit (300/100mg daily) for 7-10 days (corticosteroids: 43.6%), 39 patients |

**Per protc**

Primary Outcome

- Time to clinical response significant different between IFN b-1a and the control groups (9.8 vs. 3 days); Other outcome

- Administer of IFN b-1a before 14 days of symptom onset significantly reduces mortality (OR=13.4; CI:1.5-11) while late administration did not significantly affect outcomes (OR=2.1; CI:0.48-99)

- Hospital ICU LOS duration mechanism
### Colchicine vs. SOC

| 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.                                                                                                             |

**Ventilatio statistica different**

- Receipt IFN b-1a independent factor for survival benefit a days in multivari analysis, after adjusting IVIG and corticost receipt.

| 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 |

**Per ITT**

**Primary outcome**

- Deterior by 2 point a 7-grade scale, wi weeks or discharge higher in SOC vs. 1 Colchicine group (1.18% (OR=0.11 CI: 0.01-0.096).

**Other outcome**

- No significa differenc hospital between Colchicine SOC (me 12 vs. 13 days).

### Ruxolitinib vs. Pla

| 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 significa differenc time to c improvev in Ruxol vs. Pla g (median 15 days) (Hazard 1.669; 95% CI 0.836-3.335).

**Other outcome**

- Signific higher percenta patients showed significa improver of follow CT at day in Ruxol vs. Pla, (90% vs. 61.9%).
28-day mortality statistics different Ruxolitin Pla (0% vs 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) (Hazard ratio, 0.7 (95% CI: 0.52-2.257).
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