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Antirheumatic Disease Therapies for the Treatment of COVID-19: A Systematic Review and Meta-Analysis

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Objective. Antirheumatic disease therapies have been used to treat coronavirus disease 2019 (COVID-19) and its complications. We conducted a systematic review and meta-analysis to describe the current evidence.

Methods. A search of published and preprint databases in all languages was performed. Included studies described ≥1 relevant clinical outcome for ≥5 patients who were infected with severe acute respiratory syndrome coronavirus 2 and were treated with antirheumatic disease therapy between January 1, 2019 and May 29, 2020. Pairs of reviewers screened articles, extracted data, and assessed risk of bias. A meta-analysis of effect sizes using random-effects models was performed when possible.

Results. The search identified 3,935 articles, of which 45 were included (4 randomized controlled trials, 29 cohort studies, and 12 case series). All studies evaluated hospitalized patients, and 29 of the 45 studies had been published in a peer-reviewed journal. In a meta-analysis of 3 cohort studies with a low risk of bias, hydroxychloroquine use was not significantly associated with mortality (pooled hazard ratio [HR] 1.41 [95% confidence interval (95% CI) 0.83, 2.42]). In a meta-analysis of 2 cohort studies with some concerns/higher risk of bias, anakinra use was associated with lower mortality (pooled HR 0.25 [95% CI 0.12, 0.52]). Evidence was inconclusive with regard to other antirheumatic disease therapies, and the majority of other studies had a high risk of bias.

Conclusion. In this systematic review and meta-analysis, hydroxychloroquine use was not associated with benefit or harm regarding COVID-19 mortality. The evidence supporting the effect of other antirheumatic disease therapies in COVID-19 is currently inconclusive.

INTRODUCTION

Several antirheumatic disease therapies have emerged as potential treatments for coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2). There has been particular interest in the antimalarial agents hydroxychloroquine (HCQ) and chloroquine (1), which may inhibit SARS–CoV-2 replication by elevating endosomal pH or altering the glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor (2). After preliminary

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evidence also suggested a clinical benefit of HCQ (3), public acquisition resulted in shortages (4,5). More recently, a now-retracted study by Mehra et al demonstrated an association between HCQ use and increased mortality (6,7). Both concern for this potential risk and the aforementioned HCQ shortages have negatively impacted patients who take HCQ for rheumatic diseases.

Antirheumatic disease therapies may also mitigate the hyperinflammatory state caused by SARS–CoV-2 infection, which has been associated with elevated levels of inflammatory cytokines (8,9). Therapies that directly target the inflammatory cascade, including interleukin-6 (IL-6) inhibitors, IL-1 inhibitors, and glucocorticoids, have been widely adopted in clinical practice prior to the publication of ongoing randomized controlled trials (RCTs). Similar considerations have led to speculation that tumor necrosis factor (TNF) inhibitors and the JAK inhibitor baricitinib may be beneficial (10–12).

Recent systematic reviews have primarily focused on antimalarial therapy (13,14), and no reviews to date have included a meta-analysis of recently published large observational studies of antirheumatic disease therapies. In this systematic review and meta-analysis, we have identified and summarized published and preprint original scientific articles that describe the use of antirheumatic disease therapies for the treatment of COVID-19.

METHODS

This systematic review was performed according to the Cochrane Handbook for Systematic Reviews of Interventions (15) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (16) and the Synthesis Without Meta-Analysis guidelines (17). The protocol was registered on the International Prospective Register of Systematic Reviews (no. CRD42020176896) (18).

Data sources and literature search. A comprehensive search in any language was performed on March 17, 2020 and included all articles published between January 1, 2019 and April 1, 2020. The search was refreshed on May 7, 2020. The following databases were included: Ovid Medline and E-pub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, Web of Science, and ClinicalTrials.Gov. The search strategy was designed and conducted by an experienced librarian (LJP) with input from the study investigators. Controlled vocabulary supplemented with keywords was used to search for drug therapy for COVID-19.

Given the rapid development of new evidence, all articles available on the preprint servers medRxiv, bioRxiv, and ChinaXiv were also included. Coronavirus resource centers of *The Lancet, Journal of the American Medical Association*, and *New England Journal of Medicine* were manually searched until May 29, 2020. The studies that were identified as preprints were replaced by peer-reviewed published versions if available and identified by May 23, 2020. A detailed description of the search strategy is available in the Supplementary Materials (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41469/abstract).

Study selection eligibility criteria. Original eligibility criteria were refined after review of the initial search (18). The final eligibility criteria were as follows: 1) included ≥5 people infected with SARS–CoV-2; 2) focused on antirheumatic disease therapy (Supplementary Materials, http://onlinelibrary.wiley.com/doi/10.1002/art.41469/abstract); 3) was published after January 1, 2019; 4) was original research; 5) had one of the following outcomes: death, ventilator-free days, escalation of care (intensive care unit [ICU] transfer), length of hospital stay, symptom resolution, viral

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Table 1. Studies investigating antimalarial therapies and COVID-19 (n = 14 for HCQ and n = 5 for chloroquine)*

Medication, outcome measure, author (ref.)	Study design	n	Outcome and inference	Bias assessment†	Direction of effect‡
HCQ					
Mortality					
Rosenberg et al (26)	Cohort	1,438	No significant difference in mortality (adjusted HR 1.08 [95% CI 0.63, 1.85])	Low	QS
Magagnoli et al (27)	Cohort	368	Increased mortality in HCQ group (adjusted HR 2.6 [95% CI 1.1, 6.21])	Low	QS
Mahévas et al (28)	Cohort	173	No difference in overall survival at 21 days (weighted HR 1.2 [95% CI 0.4, 3.3]) or survival without transfer to ICU (weighted HR 0.9 [95% CI 0.4, 2.1])	Low	QS
Yu et al (66)	Cohort	568	Lower mortality in HCQ group among those critically ill (adjusted HR 0.33 [95% CI 0.17, 0.64])	High	+
Ashraf et al (67)	Case series	100	Higher rate of survival in HCQ group (OR 61.9 [95% CI 9.0, 424.7])	High	NA
Mathian et al (68)	Case series	17	2 of 14 hospitalized patients taking HCQ died	High	NA
Composite of intubation and death					
Mahévas et al (28)	Cohort	173	No difference in the combined outcome of ICU care or death (HR 0.9 [95% CI 0.4, 2.1])	Low	QS
Geleris et al (29)	Cohort	1,376	No difference in the combined outcome of IMV or death (HR 1.04 [95% CI 0.82, 1.32])	Low	QS
Escalation of care					
Magagnoli et al (27)	Cohort	368	No difference in IMV (adjusted HR 1.43 [95% CI 0.53, 3.79])	Low	–
Mathian et al (68)	Case series	17	Of 17 patients taking HCQ, 14 were admitted to hospital and 7 to ICU	High	NA
Hospital/ICU discharge					
Mahévas et al (28)	Cohort	173	No difference in discharge at 21 days (RR 1.0 [95% CI 0.9, 1.3])	Low	NA
Clinical improvement					
Tang et al (30)	RCT	150	No difference in symptom resolution at 28 days (60% vs. 67% SoC; $P = 0.97$)	High	+
Chen et al (31)	RCT	62	Shorter recovery for fever (2.2 days vs. 3.2 days; $P < 0.001$) and cough (2.0 days vs. 3.1 days; $P = 0.002$)	High	+
Mahévas et al (28)	Cohort	173	No difference in oxygen weaning at 21 days (RR 1.1 [95% CI 0.9, 1.3])	Low	+
Gautret et al (69)	Case series	80	81% with "favorable outcome" and only 15% required oxygen	High	NA
SARS–Cov-2 clearance					
Tang et al (30)	RCT	150	No difference in viral clearance at 28 days (85% vs. 81% SoC; $P = 0.34$)	High	+
Mallat et al (32)	Cohort	34	Longer duration of SARS–CoV-2 test positivity in HCQ (17 days vs. 10 days SoC; $P = 0.023$)	Some	–
Gautret et al (3)	Cohort	42	Higher rate of viral clearance at 6 days (70% vs. 13% SoC at other hospitals; $P = 0.001$)	High	+
Molina et al (70)	Case series	11	Viral load persistent 6 days after treatment in 8 of 10 patients	High	NA
Million et al (71)	Case series	1,061	Persistent SARS–CoV-2 test positivity at 10 days in 47 patients	High	NA
Gautret et al (69)	Case series	80	Viral clearance in 74 of 80 patients at 8 days	High	NA
Chloroquine					
Mortality					
Borba et al (33)	RCT	81	Higher mortality in high-dose group vs. low-dose group (log rank −2.183; $P = 0.03$)	High	–
Composite of intubation and death					
Million et al (71)	Case series	1,061	10 patients transferred to ICU and 8 patients died	High	NA
Hospital/ICU discharge					
Huang et al (34)	RCT	22	Increased likelihood of discharge in chloroquine group vs. lopinavir/ritonavir group (RR 1 [95% CI 1.33, 4])	High	+
Clinical improvement					
Huang et al (35)	Cohort	373	Shorter fever duration in the chloroquine group (1.2 days vs. 1.9 days; $P = 0.003$)	High	+

(Continued)

Table 1. (*Cont'd*)

Medication, outcome measure, author (ref.)	Study design	n	Outcome and inference	Bias assessment†	Direction of effect‡
SARS–CoV-2 clearance					
Huang et al (34)	RCT	22	Increased likelihood of negative RT-PCR on chloroquine vs. lopinavir/ritonavir (RR 1.09 [95% CI 1, 1.33])	High	+
Chen et al (36)	Cohort	284	No significant change in viral clearance with chloroquine (OR 0.7 [95% CI 0.2, 2.0])	High	+
Huang et al (35)	Cohort	373	Shorter time to viral clearance (median difference −5.4 [95% CI −6.0, −4.0]; $P < 0.001$)	High	+

* Escalation of care included intensive care unit (ICU) transfer, intubation, and mechanical ventilation. COVID-19 = coronavirus disease 2019; HCQ = hydroxychloroquine; HR = hazard ratio; 95% CI = 95% confidence interval; QS = quantitative synthesis; OR = odds ratio; NA = not applicable; IMV = invasive mechanical ventilation; RR = risk ratio; RCT = randomized controlled trial; SoC = standard of care; SARS–CoV-2 = severe acute respiratory syndrome coronavirus 2; RT-PCR = reverse transcriptase–polymerase chain reaction.
† Bias assessed using the Newcastle-Ottawa Scale for cohort studies and the Risk of Bias 2.0 tool for randomized controlled trials; case series assumed to be high risk by default.
‡ Quantified using the Cochrane vote counting method for data synthesis. Studies eligible for quantitative synthesis and case series were excluded.

clearance. Studies that did not present primary data (i.e., editorials, opinions, meta-analysis, and reviews) were excluded.

Patient research partners. Four patient research partners who have had COVID-19 (2 patients with an autoimmune disease and 2 rheumatologists) were involved throughout the project. Patient research partners participated in the selection of outcomes and the drafting of the manuscript.

Data collection process. Pairs of reviewers working independently (MP, YPEC, HT, SES, FB, MID, PK, CS-A, JS, AK, and AD-G) evaluated eligibility based on review of abstracts and titles. Records with disagreements on inclusion/exclusion were included in full-text review. Pairs of the same reviewers working independently evaluated full-text articles. Disagreements were resolved by consensus discussion and, if necessary, by involving a third reviewer. Abstract, title, and full-text review were conducted using DistillerSR software (Evidence Partners). A standardized extraction tool was developed by consensus and refined after preliminary testing on a subset of the full-text articles. The extraction tool included a full description of study characteristics, the medications patients received (dose, frequency, route), and the inferences made in each study. Pairs of reviewers extracted data independently, and differences were reconciled by the corresponding authors (MP and AD-G).

Risk of bias in individual studies. Two reviewers working independently (MP and AD-G) assessed the risk of bias. RCTs were assessed using the Risk of Bias 2.0 tool (19) and were reported using the recommended 3-item ordinal scale ("high risk of bias," "some concerns," or "low risk of bias"). Cohort studies were assessed using the Newcastle-Ottawa Scale (20). The comparability domain of the Newcastle-Ottawa Scale was the primary differentiation point for a study's risk of bias in this context and was used to determine global risk of bias (0 = high risk, 1 = some concerns, and 2 = low risk) (21). Disagreements were resolved by consensus discussion. Studies were defined as case series if they did not include an unexposed group and were deemed to have a high risk of bias by default (22,23).

Data analysis. When ≥1 study demonstrated the same outcome for the same antirheumatic therapy and showed an estimate of effect size, we performed a meta-analysis. Adjusted effect size estimates were used if available. Otherwise, unadjusted effect size estimates were used. Each study was weighted based on its log-transformed inverse variance. The meta-analysis was conducted using random-effects models due to expected clinical and methodologic heterogeneity (24). The I^2 statistic was calculated to describe heterogeneity. All analyses were conducted using RevMan 5.3 software.

We grouped the studies according to antirheumatic disease therapy and outcomes. The data were synthesized narratively and in tables. For reporting purposes and due to the methodologic diversity of the studies, we prioritized results for summary and synthesis based on study design (RCT > cohort studies > case series), risk of bias assessment (low risk > some concerns > high risk), and relevance of the outcome (e.g., mortality > viral clearance). Given the substantial heterogeneity of study design and reporting, we used the vote counting method, as described in the Cochrane handbook, to summarize the direction of the effect for a given outcome (25).

RESULTS

Study selection. The initial search was performed on March 17, 2020 and identified 1,315 studies, including 290 studies in the peer-reviewed published literature and 1,025 in preprint archives. An updated search was performed on May 7, 2020 and identified an additional 2,614 studies, including 634 studies in the published literature and 1,980 in the preprint archives. Six additional studies were identified prior to May 29, 2020 by manual search and were

included in the second extraction. After title and abstract screening, 3,660 studies were excluded. Of the 275 articles included for full-text review, 230 were excluded and 45 were included in qualitative review. One study identified by manual count was subsequently retracted (6,7) and therefore removed. Six of these studies were also eligible for meta-analysis (Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.41469/abstract).

Overall study characteristics. We included 4 RCTs, 29 cohort studies, and 12 case series. Sixteen studies had been posted to a preprint archive only, and 29 had been published in a peer-reviewed journal. Studies were conducted in China (n = 22), France (n = 10), Italy (n = 5), the US (n = 4), Brazil (n = 1), the United Arab Emirates (n = 1), Iran (n = 1), and Qatar (n = 1). All studies evaluated hospitalized patients with COVID-19 (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.41469/abstract). Of the 4 RCTs included, all had a high risk of bias. Of the 29 cohort studies, 6 had a low risk of bias, 5 had some concerns related to risk of bias, and 18 had a high risk of bias (Supplementary Tables 2 and 3, http://onlinelibrary.wiley.com/doi/10.1002/art.41469/abstract).

Antimalarial therapy. *HCQ.* Fourteen studies assessed HCQ, including 2 RCTs, 7 cohort studies, and 5 case series (Table 1). Three cohort studies (pooled n = 932) evaluated mortality and were included in quantitative synthesis (26–28). In the meta-analysis, HCQ use was not associated with a significant risk of death (pooled HR 1.41 [95% CI 0.83, 2.42]) (Figure 1A). Two cohort studies (pooled n = 1,549) were conducted to evaluate a composite risk of invasive mechanical ventilation and mortality and were included in quantitative synthesis (28,29). HCQ use was not associated with the pooled composite outcome (HR 1.03 [95% CI 0.82, 1.29]) (Figure 1B). All studies included in the quantitative synthesis had a low risk of bias.

Escalation of care and rate of discharge were each evaluated in 1 cohort study. Neither the study by Magagnoli et al assessing the risk of mechanical ventilation (27) nor one by Mahévas and colleagues evaluating discharge at 21 days (28) showed differences among patients with COVID-19 who received HCQ compared to those who did not. Both studies were considered to have a low risk of bias.

Two RCTs and 1 cohort study assessed clinical improvement. An RCT by Tang et al demonstrated no significant difference with regard to symptom alleviation at 28 days (30), while a smaller RCT by Chen et al showed a shorter recovery time with regard to both fever and cough (31). Based on vote counting, the direction of effect in both studies was toward a faster resolution of symptoms. In the aforementioned cohort study by Mahévas et al, researchers also evaluated the proportion of patients who were successfully weaned from oxygen after 21 days and found no significant difference. Both RCTs had a high risk of bias.

With regard to SARS–CoV-2 clearance, the RCT by Tang et al demonstrated no improvement in the proportion of people who had negative SARS–CoV-2 results at 28 days after treatment commenced. In a cohort study, Mallat et al found a longer duration of SARS–CoV-2 test positivity (32), while a cohort study by Gautret et al showed a higher rate of viral clearance (3). According to vote counting, there was no clear effect of HCQ on the time to viral clearance. The study by Mallat et al had some concerns about risk of bias, and the study by Gautret et al had a high risk of bias.

Chloroquine. Five studies assessed chloroquine, including 2 RCTs, 2 cohort studies, and 1 case series (Table 1). In an RCT by Borba et al, researchers assessed mortality (33), and the study was stopped early due to a safety signal that suggested a higher rate of mortality with a higher dose of chloroquine. It had a high risk of bias and did not include a placebo group as a comparator.

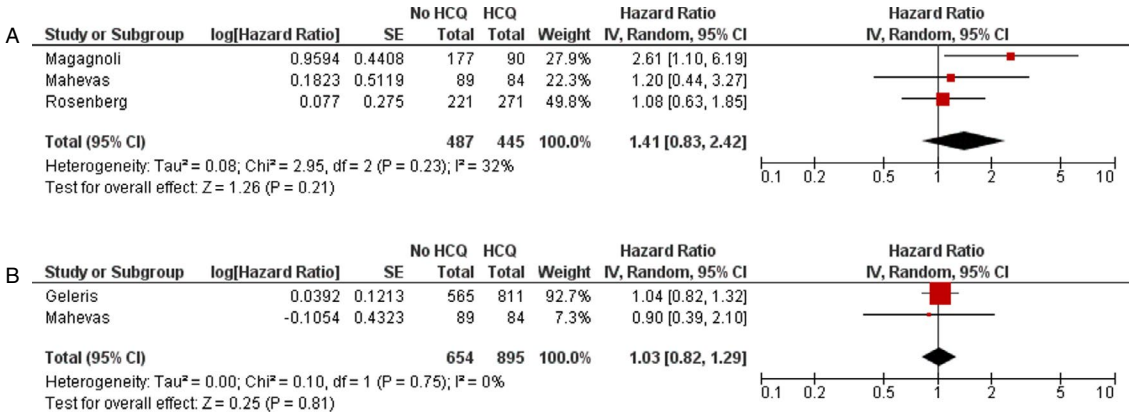

Figure 1. **A**, Meta-analysis of 3 observational studies investigating hydroxychloroquine (HCQ) and mortality among patients hospitalized with coronavirus disease 2019 (COVID-19). **B**, Meta-analysis of 2 observational studies investigating HCQ and the composite outcome of death or intubation among patients hospitalized with COVID-19. IV = inverse variance; 95% CI = 95% confidence interval.

Table 2. Studies investigating IL-6 inhibitors and COVID-19 (n = 7 for TCZ and n = 1 for siltuximab)*

Outcome measure, author (ref.)	Study design	n	Outcome and inference	Bias assessment†	Direction of effect‡
Mortality					
Roumier et al (37)	Cohort	59	No difference in mortality in TCZ group (17.2% vs. 18.7% SoC; *P* = 0.837)	Some	+
Quartuccio et al (39)	Cohort	111	Higher mortality in TCZ group (9.5% vs. 0% SoC)	High	–
Klopfenstein et al (38)	Cohort	45	Numerically lower mortality in TCZ group (25% vs. 48% historical SoC; *P* = 0.07)	High	+
Sciascia et al (72)	Case series	63	Mortality of 11% at day 14; increased survival with early TCZ (HR 2.2 [95% CI 1.3, 6.7])	High	NA
Luo et al (73)	Case series	15	Death in 3 of 15 patients (20%) treated with TCZ at 1 week of follow-up	High	NA
Alattar et al (74)	Case series	25	Death in 3 of 25 patients (12%) treated with TCZ at day 14	High	NA
Gritti et al (75)	Case series	21	IMV or death in 5 of 21 patients (24%) treated with siltuximab	High	NA
Composite of intubation and death					
Klopfenstein et al (38)	Cohort	45	Lower death/ICU admission in TCZ group (25% vs. 72% historical SoC; *P* = 0.002)	High	+
Escalation of care					
Roumier et al (37)	Cohort	59	Lower rate of IMV in TCZ group (adjusted OR 0.42 [95% CI 0.2, 0.9])	Some	+
Klopfenstein et al (38)	Cohort	45	Lower rate of IMV in TCZ group (0% vs. 32% historical SoC; *P* = 0.006)	High	+
Hospital/ICU discharge					
Klopfenstein et al (38)	Cohort	45	No difference in hospital discharge rate with TCZ (55% vs. 44% historical SoC; *P* = 0.453)	High	+
Alattar et al (74)	Case series	25	Discharge after improvement from ICU at day 14 in 9 of 25 patients (36%) treated with TCZ	High	NA
Clinical improvement					
Quartuccio et al (39)	Cohort	111	Lower rate of "complete" recovery in TCZ group (21% vs. 100% SoC)	High	–
Sciascia et al (72)	Case series	63	Pao_2:Fio_2 improved (152 ± 53 day 0; 284 ± 116 day 7; 302 ± 126 day 14; *P* < 0.05)	High	NA
Gritti et al (75)	Case series	21	Improvement in 7 of 21 patients (33%) treated with siltuximab	High	NA
Xu et al (76)	Case series	21	Improved oxygenation in 15 of 20 patients (75%) and discharge in 21 of 21 patients (100%) treated with TCZ	High	NA

* Escalation of care included ICU transfer, intubation, and mechanical ventilation. IL-6 = interleukin-6; TCZ = tocilizumab; Pao_2:Fio_2 = arterial partial pressure oxygen to fractional inspired oxygen ratio (see Table 1 for other definitions).
† Bias assessed using the Newcastle-Ottawa Scale; case series assumed to be high-risk by default.
‡ Quantified using the Cochrane vote counting method for data synthesis. Studies eligible for quantitative synthesis and case series were excluded.

An RCT by Huang et al that compared chloroquine to lopinavir/ritonavir demonstrated that participants receiving chloroquine were twice as likely to be discharged (34), and a cohort study by Huang et al showed a significantly shorter duration of fever in the chloroquine group (35). The same 2 studies also addressed SARS–CoV-2 clearance. The RCT showed a higher likelihood of clearance with chloroquine compared to ritonavir/lopinavir, while the cohort study showed a shorter time for viral clearance. In another cohort study, Chen et al found no significant change in viral clearance at 14 days (36). All studies assessing viral clearance had a high risk of bias and, according to vote counting, had the same direction of effect toward a shorter time for viral clearance.

IL-6 inhibitors. Seven studies assessed tocilizumab, an IL-6 receptor inhibitor, including 3 cohort studies and 4 case series; 1 case series assessed the IL-6 inhibitor siltuximab (Table 2). Three cohort studies assessed mortality. Roumier et al found no difference after adjustment (37), Klopfenstein et al found a numerically lower mortality rate (38), and Quartuccio et al found a numerically higher mortality rate with tocilizumab (39). The cohort studies by Roumier et al and Klopfenstein et al showed a significantly lower rate of escalation of care to mechanical ventilation, while the cohort study by Quartuccio et al described a lower rate of "complete" recovery among tocilizumab users. In the study by Roumier et al, there were some concerns regarding risk of bias, and the studies by Quartuccio et al and Klopfenstein et al both had a high risk of bias.

Table 3. Studies investigating GCs and COVID-19 (n = 14)*

Outcome measure, author (ref.)	Study design	n	Outcome and inference	Bias assessment†	Direction of effect‡
Mortality					
Fadel et al (42)	Cohort	213	Lower mortality with early GC protocol (14% vs. 26%; *P* = 0.024; OR 0.5 [95% CI 0.2, 0.9])	Some	+
Lu et al (77)	Cohort	244	No difference in mortality (adjusted HR 1.1 [95% CI 0.2, 7.4])	Some	–
Wu et al (78)	Cohort	201	Reduced mortality in patients with ARDS (HR 0.38 [95% CI 0.2, 0.7])	Some	+
Shi et al (79)	Cohort	101	No difference in mortality at 3 days (51% survived vs. 35% died; *P* = 0.12)	High	+
Liu et al (49)	Cohort	109	No difference in survival (*P* = 0.56; effect not available)	High	–
Qi et al (51)	Cohort	21	In people with cirrhosis, lower rate of GC use in survivors (3 of 16 [19%]) vs. nonsurvivors (5 of 5 [100%])	High	–
Wang et al (41)	Cohort	46	No difference in mortality with methylprednisolone (7.7% vs. 5.0% SoC; *P* = 0.71)	High	–
Jacobs et al (80)	Cohort	221	No association with GCs and ICU mortality (9.5 days vs. 11.0 days discharge; *P* = 0.21)	High	–
Cao et al (50)	Cohort	102	No difference in GCs among survivors (47%) and nonsurvivors (65%) (*P* = 0.18)	High	–
Composite of intubation and death					
Wang et al (40)	Cohort	115	No difference in ICU admission or mortality (OR 2.2 [95% CI 0.5, 9.4])	High	–
Escalation of care					
Fadel et al (42)	Cohort	213	Lower progression to IMV with early GC protocol (22% vs. 37%; *P* = 0.025)	Some	+
Wang et al (41)	Cohort	46	Lower rate of ventilation in methylprednisolone group (12% vs. 35% SoC; *P* = 0.05)	High	+
Hospital/ICU discharge					
Fadel et al (42)	Cohort	213	No difference in hospital discharge (67% vs. 62%; *P* = 0.58)	Some	–
Wang et al (41)	Cohort	46	Shorter hospitalization in methylprednisolone group (14 days [IQR 11–6] vs. 22 days [IQR 18–26]; *P* < 0.001)	High	+
SARS–CoV-2 clearance					
Chen et al (44)	Cohort	25	No difference in viral clearance (43% clearance vs. 73% no clearance; *P* = 0.23)	High	–
Fang et al (45)	Cohort	78	No change in time to viral clearance (17.6 ± 4.9 days vs. 18.7 ± 7.7 days with no GCs)	High	+
Ling et al (43)	Cohort	66	Longer time to viral clearance (15 days vs. 8 days; *P* = 0.01)	High	–
Chen et al (81)	Case series	97	No difference in time to negative conversion (10.0 days vs 10.0 days; *P* > 0.05)	High	NA

* Escalation of care included ICU transfer, intubation, and mechanical ventilation. GCs = glucocorticoids; ARDS = acute respiratory distress syndrome; IQR = interquartile range (see Table 1 for other definitions).
† Bias assessed using the Newcastle-Ottawa Scale; case series assumed to be high-risk by default.
‡ Quantified using the Cochrane vote counting method for data synthesis. Studies eligible for quantitative synthesis and case series were excluded.

Glucocorticoids. Fourteen studies assessed glucocorticoid use, including 13 cohort studies and 1 case series (Table 3). Nine cohort studies evaluated mortality and glucocorticoids. There was variability regarding timing of glucocorticoid use and COVID-19 disease severity. Based on vote counting, the direction of effect was positive in one-third of the studies and negative in the remaining two-thirds. One cohort study by Wang et al showed no difference in a composite outcome of ICU admission or mortality (40). Two cohort studies both demonstrated a lower rate of escalation of care (41,42). The study by Wang et al (41) showed a shorter hospitalization time with methylprednisolone, but the cohort study by Fadel (42) et al did not. Three cohort studies evaluated SARS–CoV-2 clearance with glucocorticoids. One study showed a significantly increased time to viral clearance (43), and 2 studies showed no significant difference (44,45). Eleven of the 14 studies had a high risk of bias.

Anakinra. Three studies assessed the IL-1 inhibitor anakinra, including 2 cohort studies and 1 case series (Table 4). The 2 cohort studies (pooled n = 141) evaluated mortality and were included in the quantitative analysis (46,47). Anakinra was associated with a significantly lower risk of mortality (pooled HR 0.25 [95% CI 0.12, 0.52]), compared to the standard of care (Figure 2). Huet et al (46) also

Table 4. Studies investigating other antirheumatic therapies and COVID-19 (n = 3 for anakinra, n = 4 for IVIG, and n = 1 for baricitinib)*

Medication, outcome measure, author (ref.)	Study design	n	Outcome and inference	Bias assessment†	Direction of effect‡
Anakinra					
Mortality					
Huet et al (46)	Cohort	96	Anakinra associated with lower rate of death (HR 0.3 [95% CI 0.1, 0.7])	Some	QS
Cavalli et al (47)	Cohort	52	High-dose anakinra (5 mg/kg BID) associated with lower mortality at 21 days (HR 0.2 [95% CI 0.04, 0.63])	High	QS
Composite of intubation and death					
Huet et al (46)	Cohort	96	Anakinra associated with lower rate of composite IMV/death (HR 0.2 [95% CI 0.1, 0.5])	Some	+
Escalation of care					
Huet et al (46)	Cohort	96	Anakinra associated with lower rate of invasive mechanical ventilation (HR 0.2 [95% CI 0.1, 0.6])	Some	+
Cavalli et al (47)	Cohort	52	No difference in high-dose anakinra and IMV-free survival at 21 days (HR 0.5 [95% CI 0.2, 1.3])	High	+
Clinical improvement					
Aouba et al (82)	Case series	9	9 of 9 patients treated with anakinra improved	High	NA
IVIG					
Mortality					
Shao et al (48)	Cohort	325	Lower 60-day mortality with IVIG (HR 0.3 [95% CI 0.1, 0.6])	Some	+
Liu et al (49)	Cohort	109	No difference in survival with IVIG (P = 0.51; effect not available)	High	–
Qi et al (51)	Cohort	21	No difference in survival with IVIG (P = 0.063)	High	–
Cao et al (50)	Cohort	102	No difference in IVIG among survivors (6%) and nonsurvivors (0%) (P = 0.68)	High	+
Baricitinib					
Escalation of care					
Cantini et al (52)	Cohort	24	No difference in ICU transfer at week 2 with baricitinib (0% vs. 33% SoC; P = 0.09)	High	+
Hospital/ICU discharge					
Cantini et al (52)	Cohort	24	Higher rate of discharge at week 2 with baricitinib (58% vs. 8% SoC; P = 0.03)	High	+

* Escalation of care included ICU transfer, intubation, and mechanical ventilation. IVIG = intravenous immunoglobulin; BID = twice daily (see Table 1 for other definitions).
† Bias assessed using the Newcastle-Ottawa Scale; case series assumed to be high-risk by default.
‡ Quantified using the Cochrane vote counting method for data synthesis. Studies eligible for quantitative synthesis and case series were excluded.

found a lower rate of a composite end point of mechanical ventilation or death, but Cavalli and colleagues (47) did not find a difference with regard to ventilator-free survival at 21 days. The study by Cavalli et al had a high risk of bias, while there were some concerns related to the risk of bias in the study by Huet et al.

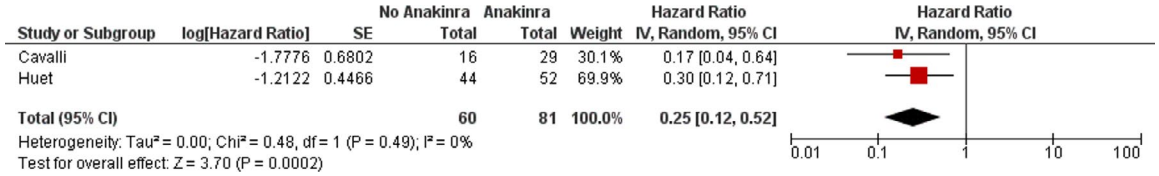

Figure 2. Meta-analysis of 2 observational studies investigating anakinra and mortality among patients hospitalized with COVID-19. See Figure 1 for definitions. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.41481/abstract.

Intravenous immunoglobulin (IVIG). Four cohort studies evaluated mortality and the use of IVIG (Table 4). One study demonstrated a lower risk of mortality at 60 days with IVIG, while 2 other cohorts demonstrated no difference in survival (48–50). In a study of patients with cirrhosis and COVID-19, there was no difference in mortality between patients receiving and those not receiving IVIG (51). The direction of effect was split evenly according to vote counting. There were some concerns pertaining to the risk of bias in the cohort study by Shao et al, and the other 3 studies had a high risk of bias.

Baricitinib. One cohort study with a high risk of bias showed no significant difference in ICU transfer at 2 weeks, but there was higher rate of discharge at week 2 among patients who received baricitinib (52) (Table 4).

DISCUSSION

In this systematic review and meta-analysis of antirheumatic disease therapies for the treatment of COVID-19, the use of HCQ was not associated with mortality. The effects of other antirheumatic disease therapies were frequently contradictory with respect to mortality, escalation of care, discharge, clinical improvement, and SARS–CoV-2 clearance. This may reflect important limitations of the included studies, the majority of which had small sample sizes and inadequate or absent comparator groups. Many also relied upon viral clearance as their primary outcome measure, a surrogate measure that may not be clinically relevant. These results extend recent systematic reviews of HCQ (13,14) to a broader range of antirheumatic disease therapies and complement guidance from the American College of Rheumatology that focused on patients with rheumatic diseases (53).

Despite limitations of the available evidence, patterns have begun to emerge. Contrary to early enthusiasm for HCQ (1,4), in this meta-analysis, HCQ use was not associated with a mortality benefit in people with COVID-19. These findings are consistent with general observations from another systematic review (13) and from a recently published RCT that assessed postexposure prophylaxis (54). In contrast to reported findings from a now-retracted study by Mehra et al (6,7), HCQ use was not associated with increased mortality. This may reassure patients with rheumatic diseases, who were understandably concerned about taking HCQ after these apparently unverifiable data were published. Definitive data from large randomized trials are expected to be published soon, including the National Institutes of Health–sponsored ORCHID trial, the RECOVERY trial from the UK, and the World Health Organization Solidarity trial. All 3 trials recently halted enrollment and have shown a lack of benefit as reported in press releases (55–57). Overall, our findings and other data support a growing consensus that antimalarial therapies for COVID-19 should be limited to use in ongoing clinical trials (58,59).

Therapies that target the hyperinflammatory state of COVID-19, including IL-1 and IL-6 inhibitors, have been widely used despite a relative paucity of data. Results from our meta-analysis of 2 studies showed an association between anakinra and lower mortality, but this should be interpreted with caution. One study did not adequately control for confounders, and the other study used a historical cohort as a comparator group (46,47). Neither study provided adequate evidence to support widespread use of drugs inhibiting IL-1 for treatment of COVID-19, which must await high-quality evidence from ongoing RCTs. The available data for IL-6 inhibition were similarly limited. Few studies of IL-6 inhibitors used an adequate comparator, and the results of IL-6 inhibitor studies were frequently conflicting. It should be noted that both IL-1 and IL-6 inhibitors were typically used for patients with moderate-to-severe acute respiratory distress syndrome. Selection bias, publication bias, and confounding by indication may have influenced purported associations. Press releases from ongoing RCTs have been encouraging, but peer-reviewed data will be essential in determining the role of these therapies.

Glucocorticoids have also been widely used in hospitalized patients with COVID-19. As with IL-1 and IL-6 inhibitors, they typically have been reserved for patients with moderate-to-severe disease, likely biasing risk estimates. Overall, no definitive conclusions could be drawn from our data synthesis. Small studies with inadequate or absent comparator groups generally suggested no difference with regard to mortality. Those that included a comparator had conflicting findings, and none were assessed as having a low risk of bias. After the final date of our search, preliminary findings from the adaptive RECOVERY trial, which assessed dexamethasone in hospitalized patients with COVID-19, were published (60). The RECOVERY trial was well designed and showed a significant reduction in mortality at 28 days in patients randomized to receive open-label dexamethasone as opposed to usual care (age-adjusted rate ratio 0.83 [95% CI 0.74, 0.92]). These data support current recommendations for prescribing glucocorticoids in a select group of patients with COVID-19 (58,61,62).

IVIG and baricitinib have also been studied. One study with an inadequate comparator showed an association between IVIG use and lower mortality at 60 days. Only 1 small cohort study with a high risk of bias evaluated baricitinib. It demonstrated no difference with respect to escalation of care, but patients who received baricitinib were more likely to be discharged at 2 weeks. Although it did not meet inclusion criteria, we identified 1 case series of eculizumab use in 4 patients (63), all of whom recovered.

Our search did not identify any studies as of May 29, 2020 that evaluated other antirheumatic disease therapies, such as colchicine or TNF inhibitors. Clinical trials are underway to further assess IVIG, baricitinib, and eculizumab, among others (63–65).

Strengths of this review were a rigorous application of systematic review methodology and a comprehensive search of the literature, which included published and preprint archives

in all languages. Another strength was the inclusion of patients with rheumatic diseases and patients with COVID-19 in the review process. In fact, several members of the review team contracted COVID-19 during the execution of this review.

Our study also had a number of limitations. First, the COVID-19 literature has rapidly expanded and indexing may be delayed, which makes performing a systematic review difficult. At the time of this writing (June 10, 2020), we are not aware of any consequential publications that have been missed. Second, although we used validated risk of bias assessments with 2 reviewers working in parallel, such judgments may be open to interpretation, and use of other validated tools may have led to different conclusions. Third, all of the observational data came from hospitalized patients and may not be generalizable to a broader population. This highlights an important limitation of the literature itself, as we found no studies of outpatients infected with COVID-19 who received antirheumatic disease therapies. Finally, the degree to which publication bias has influenced the current literature was not assessed, but preprint archives were included to mitigate such biases.

These limitations notwithstanding, this comprehensive systematic review and meta-analysis suggests that HCQ use is not associated with benefit or harm with regard to COVID-19 mortality. Antirheumatic disease therapies should be investigated further in RCTs. In the interim, physicians should be cautious in offering off-label antirheumatic disease therapies to patients with COVID-19 based on the currently available literature.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Putman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Putman, Chock, Tam, Kim, Sattui, Berenbaum, Danila, Korsten, Sanchez-Alvarez, Sparks, Coates, Palmerlee, Peirce, Jayatilleke, Johnson, Kilian, Liew, Prokop, Grainger, Wallace, Duarte-García.

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Analysis and interpretation of data. Putman, Chock, Tam, Kim, Sattui, Berenbaum, Danila, Korsten, Sanchez-Alvarez, Sparks, Jayatilleke, Johnson, Kilian, Liew, Murad, Grainger, Wallace, Duarte-García.

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