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Pharmacological therapies for patients with human coronavirus infections: a rapid systematic review

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Abstract *This work aimed to evaluate the effects of drug therapies for coronavirus infections. Rapid systematic review with search in the MEDLINE, EMBASE, Cochrane, BVS, Global Index Medicus, Medrix, bioRxiv, Clinicaltrials.gov and International Clinical Trials Registry Platform databases. Thirty-six studies evaluating alternative drugs against SARS, SARS-CoV-2 and MERS were included. Most of the included studies were conducted in China with an observational design for the treatment of COVID-19. The most studied treatments were with antimalarials and antivirals. In antimalarial, the meta-analysis of two studies with 180 participants did not identify the benefit of hydroxychloroquine concerning the negative viral load via real-time polymerase chain reaction, and the use of antivirals compared to standard care was similar regarding outcomes. The available scientific evidence is preliminary and of low methodological quality, which suggests caution when interpreting its results. Research that evaluates comparative efficacy in randomized, controlled clinical trials, with adequate follow-up time and with the methods properly disclosed and subject to scientific peer review is required. A periodic update of this review is recommended.*

Key words *Coronavirus, Coronavirus Infections, Severe Acute Respiratory Syndrome, Therapeutics, Systematic Review*

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Introduction

The outbreak of pneumonia cases, which initially occurred in Hubei, China, evolved into the 2019 Coronavirus Disease pandemic (COVID-19)[1]. The disease is caused by the Coronavirus-2 of severe acute respiratory syndrome (SARS-CoV-2)[2]. The World Health Organization (WHO) has declared strategic objectives on the pandemic, among them responding to critical knowledge gaps about the therapeutic options[2] available for coronavirus infections.

Understanding the complete natural history of COVID-19 is evolving. The WHO[3] published the provisional guidelines. In the clinical presentation, pneumonia seems to be the most severe frequent manifestation of the infection, characterized mainly by fever, dry cough, dyspnea, and bilateral infiltrates in chest imaging tests[4-7]. As of April 2020, there no vaccines or specific treatments were available for human coronavirus infections.

Given the developing coronavirus situation, policymakers urgently require a synthesis of evidence to make decisions and guide the population. Rapid evidence synthesis is recommended by WHO[8] in circumstances like these. Thus, this study aims to evaluate the effects of drug therapies for coronavirus infections.

Methods

Design and protocol registration

A quick, systematic review of the literature was carried out, a secondary study that gathers the available evidence on a topic, carried out swiftly, to meet the decision-makers' demand in a timely fashion[9]. The study was conducted to scientifically and impartially inform the decision-making in the health of managers of the Brazilian Ministry of Health in the context of the public health emergency of national importance, COVID-19. The study protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) platform. The report of this review is in line with the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Eligibility criteria

Studies of systematic reviews, randomized clinical trials, cohorts, case-controls, and case series that evaluated the effects of alternative drug therapies for infection by any type of human coronavirus were included. We excluded studies that contained data that could not be extracted completely, overlapping data between studies, book chapters, letters to the editor, posters, editorials, modeling, guidelines or country guides, studies carried out on animals, or *in silico*.

Information sources and search strategies

A bibliographic search was performed in the sources of Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Cochrane Library, and Virtual Health Library (BVS). The lists of bibliographic references of the relevant studies were examined to identify possible eligible studies. A search was also conducted on the Global Index Medicus, Medrix, and bioRxiv, as well as free search on the websites of the governments of countries with confirmed cases and clinical trial, records through the Clinicaltrials.gov and International Clinical Trials Registry Platform (ICTRP) databases. There were no restrictions on the participants' age, language, status, and year of publication.

The search was updated until April 21, 2020. The search strategy was developed by one researcher and independently reviewed by another researcher. The following search strategy was used to search in Medline, being adapted for the other databases: (("coronavirus"[mesh] or "cov"[all fields] or "coronavirus infections"[mesh] or "wuhan coronavirus"[all fields] or "human coronavirus"[all fields] or "coronavirus nl63, human"[mesh] or "coronavirus oc43, human"[mesh] or "coronavirus 229e, human"[mesh] or covid-19[all fields] or "new coronavirus" [all fields] or 2019-ncov[all fields] or "novel coronavirus" [all fields] or betacoronavirus[all fields]) and ("antiviral agents"[mesh] or "therapeutics"[mesh] or drug[all fields] or "emergency treatment"[mesh])) and "treatment outcome"[mesh terms] (("coronavirus"[mesh] or "cov"[all fields] or "coronavirus infections"[mesh] or "wuhan coronavirus"[all fields] or "human coronavirus"[all fields] or "coronavirus nl63, human"[mesh] or "coronavirus oc43, human"[mesh] or "coronavirus 229e, human"[mesh] or covid-19[all fields] or "new coronavirus" [all fields] or 2019-ncov[all fields] or "novel coronavirus" [all fields] or betacoronavirus[all fields]) and ("antiviral agents"[mesh] or "therapeutics"[mesh] or drug[all fields] or

"emergency treatment"[mesh])) and "treatment outcome"[mesh terms].

Data collection process

The Rayyan system[10] was adopted for the selection of studies and data extraction. After removing duplicate records, two reviewers independently selected paper by title and abstract, as per pre-defined eligibility criteria. The selected works were independently read in full by two authors. In both stages, any case disagreement was resolved by a third reviewer. The following data were extracted: author, year of publication, country, study design, age (mean years), type of coronavirus, sample size, proportion of men (%), funding sources, intervention, comparator, and (clinical, laboratory) outcomes.

Methodological quality assessment

The evaluation of the methodological quality and the risk of bias of the included studies was carried out independently by six researchers, using appropriate tools for each study design, as follows: a) systematic reviews: A MeaSurement Tool to Assess Reviews (AMSTAR 2)[11]; b) randomized clinical trial: Cochrane bias risk assessment[9]; c) cohort and case series: Joanna Briggs Institute tools[12].

Summary of results and statistical analysis

The outcomes assessed in this review were mortality rate, clinical outcomes (length of hospital stay, length of ICU stay, need for non-invasive mechanical ventilation, need for oxygen therapy, adverse events, body temperature), and detection of viral RNA (RT-PCR). The results of the included studies were presented descriptively. Data on outcomes evaluated by the included studies were reported considering the size of effect estimates (relative risk, absolute risk difference, odds ratio, the number required to treat, and others) and their respective confidence and variance measures (a measure of dispersion, confidence intervals, and p-values).

Due to the limited number of studies reporting similar results for infections, the meta-analysis was conducted only for two studies on hydroxychloroquine against SARS-CoV-2. A meta-analysis using the Mantel-Hazel method for dichotomous data with the random-effects model was chosen a priori. Risk ratio (RR) was used for timely estimation together with the 95% confidence interval. The chi-square test was applied to measure heterogeneity between studies with a significance level of $p < 0.05$. The magnitude of the inconsistency was measured using the I-square (I^2) statistics. High heterogeneity was considered when I^2 was above 75%, moderate when it was between 55% and 75%, and low when I^2 was below 25%. RevMan version 5.3 was used for the analysis.

Results

Selection of studies

We identified 2,259 records, of which 91 were duplicated. After screening titles and abstracts, 68 records were selected for full-text reading. Of these, 36 met the eligibility criteria and were included in this review. The details of the selection process are illustrated in Figure 1.

Main characteristics of the included studies

The main characteristics of the included studies are shown in Chart 1. Most of the 36 included studies were retrospective cohorts and conducted in China, and published between 2018 and 2020. The mean age of patients was 48 years, and most of these people were diagnosed with SARS-CoV-2 infection or severe acute coronavirus syndrome (SARS-CoV) through real-time polymerase chain reaction (RT-PCR). Studies with patients with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) were also included. The effects of coronavirus drug therapies are described in Chart 2.

Antimalarials

Four randomized controlled trials (RCTs)[13-16], two retrospective cohorts[17,18], a prospective cohort[19], and three case series[20-22] evaluated the use of hydroxychloroquine (HCQ) or chloroquine (CQ) for SARS-CoV-2. Four studies compared HCQ with standard treatment[13,14,16,19]. Three studies evaluated the time to clinical improvement[13,14,16]. In one RCT[13], the time to normalize body temperature was similar between the groups, while treatment with HCQ resulted in less time in two other RCTs[14,16]. In a single study[14], the number of days of cough was significantly less in the HCQ group. Two RCTs[14,16] evaluated the negative viral load by RT-PCR on the seventh day after starting therapy. The meta-analysis

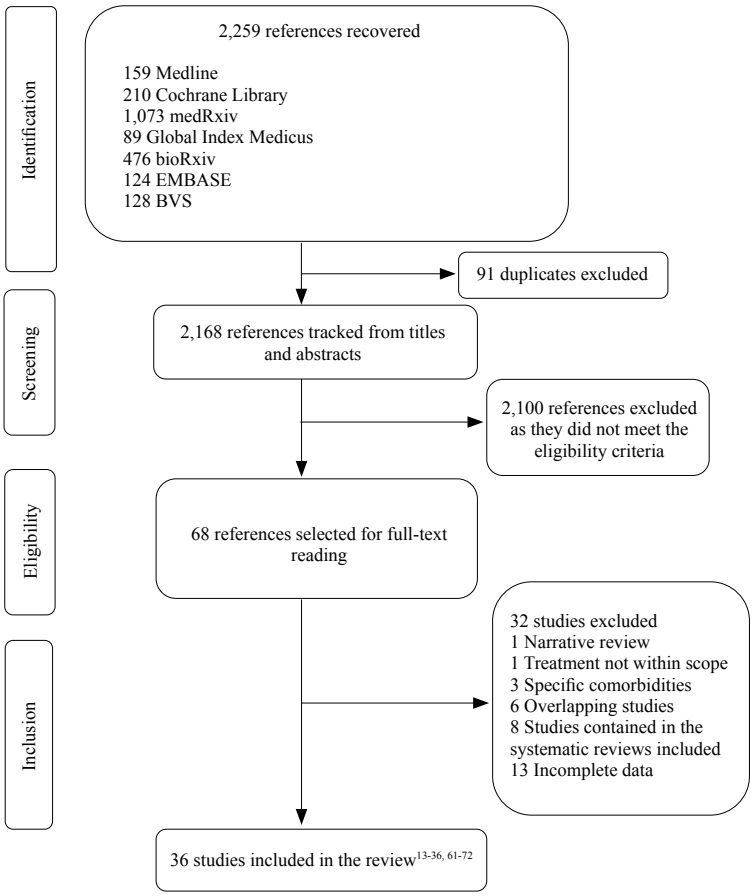

Figure 1. Process of search, selection and inclusion of studies.

found no significant difference in the probability of negative viral load by RT-PCR between the HCQ group and the group that received conventional treatment (RR = 0.94; 95%CI: 0.78-1.13; 180 participants; $I^2 = 0\%$) (Figure 2).

Moreover, a cohort[19] had a significantly lower proportion of patients with negative RT-PCR in the HCQ group. A cohort[18] showed that the HCQ group has a higher risk of death from any cause when compared to the group without HCQ. However, another cohort[17] found no difference between the groups.

Five studies investigated the effects of HCQ associated with azithromycin (AZT) compared to standard treatment[17-21]. In a cohort[19], the proportion of patients with negative RT-PCR was significantly lower in the HCQ group. On the other hand, the therapeutic combination had no significant effect in case series[20]. Another case series[21] with 80 participants evidenced a negative virological result in 83% of patients who used HCQ on day 7 of follow-up, and in 93% on day 8. The mortality rate was assessed in two cohorts. In the first one[18], it was worse in the group treated with HCQ and AZT, and in the other[17], no differences were observed between groups. In one of the case series[21], patients had nausea, vomiting, diarrhea, and blurred vision. In two other case series[20,22], patients had persistent QT interval prolongation.

An RCT[15] compared the use of CQ administered at different dosages. Preliminary results suggest that the high-dose QC regimen (12g administered over 10 days) was not safe. The authors canceled the tests when they found that one quarter of the patients tested with a high-dose of QC showed persistent QT prolongation above 500ms and higher lethality.

Chart 1. Main characteristics of the studies included in the review (n=36).

Author, year of publication	Country	Study design	Age (mean years)	Coronavirus type	Diagnosis	Sample size	Funding sources
Antimalarial							
Chen J et al.[13] (2020)	China	Randomized clinical trial	50.5	SARS-CoV-2	RT-PCR	30	Shanghai Public Health Clinical Center
Chen Z et al.[14] (2020)	China	Randomized clinical trial	44.7	SARS-CoV-2	RT-PCR	62	Department of Hubei Province
Borba et al.[15] (2020)	Brazil	Randomized clinical trial	51.1	SARS-CoV-2	Suspected clinical-epidemiological cases (23.3%) and cases confirmed by RT-PCR (76.7%)	81	Público (Government of Amazonas, Farmanguinhos-Fiocruz, Superintendency of the Free Zone of Manaus, Coordination for the Improvement of Higher Education Personnel, Research Support Foundation of the State of Amazonas, Federal Senate funds)
Tang et al.[16] (2020)	China	Randomized clinical trial	46.0	SARS-CoV-2	RT-PCR	150	Emerging National Science and Technology Projects, China National Natural Science Foundation and others
Mahévas et al.[17] (2020)	France	Retrospective cohort	60.0	SARS-CoV-2	RT-PCR	198	No funding
Magagnoli et al.[18] (2020)	USA	Retrospective cohort	70.0	SARS-CoV-2	RT-PCR	368	National Institutes of Health (USA) grants and DuPont Guerry, III, Professorship, and University of Virginia Strategic Investment Fund to JA
Gautret et al.[19] (2020)	France	Prospective Cohort	51.2	SARS-CoV-2	RT-PCR	42	Public (French Government)
Chorin et al.[22] (2020)	USA	Case series	63.0	SARS-CoV-2	RT-PCR	84	Not declared
Gautret et al.[21] (2020)	France	Case series	52.0	SARS-CoV-2	RT-PCR	80	Public (French Government)
Molina et al.[20] (2020)	France	Case series	58.7	SARS-CoV-2	RT-PCR	11	Not declared
Antivirals and Antiretrovirals							
Li et al.[23] (2020)	China	Randomized clinical trial	49.7	SARS-CoV-2	RT-PCR	86	Guangzhou High Level Clinical Infectious Disease Specialty
Young et al.[25] (2020)	Singapore	Case series	47	SARS-CoV-2	PCR	18	Singapore National Medical Research Council

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Chart 1. Main characteristics of the studies included in the review (n=36). (continuation)

Author, year of publication	Country	Study design	Age (mean years)	Coronavirus type	Diagnosis	Sample size	Funding sources
Cao et al.[24] (2020)	China	Randomized clinical trial	58.0	SARS-CoV-2	Reverse transcriptase-polymerase chain reaction (RT-PCR)	199	Not informed
Immunomodulators							
Zhou et al.[26] (2020)	China	Retrospective cohort	48.0	SARS-CoV-2	RT-PCR	77	No funding
Anticoagulant							
Negri et al.[27] (2020)	Brazil	Case series	56.0	SARS-CoV-2	RT-PCR	27	No funding
Shi C et al.[28] (2020)	China	Retrospective cohort	69.0	SARS-CoV-2	RT-PCR	42	National Natural Science Foundation of China
Corticoid							
Arabi et al.[29] (2018)	Saudi Arabia	Retrospective cohort	57.8 SD 17.2	MERS-CoV	RT-PCR	309	Not informed
Wang et al.[30] (2020)	China	Retrospective cohort	54.0 (IQR) 48-64	SARS-CoV-2	RT-PCR	46	Natural Science Foundation of China
Lu et al.[31] (2020)	China	Retrospective cohort	57.0	SARS-CoV-2	Not reported	244	National R&D Program, China
Auyeung et al.[32] (2005)	China	Retrospective cohort	47.7 SD 19.9	SARS-CoV	RT-PCR	78	Not informed
Combined therapies							
Morra et al.[34] (2018)	Saudi Arabia, France, Greece and Qatar	Systematic review and meta-analysis with 16 studies	57.6	MERS-CoV	RT-PCR PCR	116	Japan Ministry of Education, Culture, Sports, Science and Technology
Al-Tawfiq e Memish[61] (2017)	Undefined	Systematic review with 14 studies	Not informed	MERS-CoV	RT-PCR PCR	128	Not informed
Momattin et al.[62] (2013)	Undefined	Systematic review with 19 studies	Not informed	SARS-CoV	RT-PCR PCR	1049	Not informed
Chiou et al.[35] (2005)	China	Retrospective cohort	38 SD 17.5	SARS-CoV	PCR	51	Taiwan National Science Council National SARS-CoV Research Program
Lau et al.[63] (2004)	China	Prospective cohort	42.5 SD 14.8	SARS-CoV	PCR	71	Not informed
Chen X et al.[64] (2020)	China	Retrospective cohort	48	SARS-CoV-2	RT-PCR	280	Natural Science Foundation of China

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Chart 1. Main characteristics of the studies included in the review (n=36). (continuation)

Author, year of publication	Country	Study design	Age (mean years)	Coronavirus type	Diagnosis	Sample size	Funding sources
Bian et al.[33] (2020)	China	Clinical trial	51	SARS-CoV-2	*According to diagnosis and treatment guidelines (Diagnosis and Treatment for 2019 Novel Coronavirus Disease)*	18	*National Science and Technology Project*
Shi Q et al.[65] (2020)	China	Retrospective cohort	71	SARS-CoV-2	*World Health Organization interim guidance*	101	*National Natural Science*
Jiang et al.[66] (2020)	China	Retrospective cohort	45	SARS-CoV-2	*According to Chinese management guideline (7th Edition)*	55	*Wuxi Municipal Health Commission Major, Wuxi Science and Technology Bureau COVID-19 special project, Wuxi Science e Technology Bureau guiding plan*
Hu et al.[67] (2020)	China	Retrospective cohort	61	SARS-CoV-2	*According to WHO interim guidance and guidelines of COVID-19 diagnosis and treatment trial 5th Edition, by the National Health Commission of the People's Republic of China*	323	*Natural Science Foundation of Hubei Province e the Top Youth Talent Program in Hubei Province*
Duan et al.[68] (2020)	China	Case series	52.5	SARS-CoV-2	RT-PCR	10	Chinese Ministry of Science and Technology
Chen H et al.[69] (2020)	China	Clinical trial	not reported (median of 31 in the intervention group and 44 in the control group)	SARS-CoV-2	RT-PCR	11	*Partial funding by the Science and Technology Bureau of Nanchang City Shanghai Guangxi Translational Medicine Development Foundation*
Tsui et al.[70] (2003)	China	Retrospective cohort	41 SD 14	SARS-CoV	RT-PCR	323	Not informed
Yan et al.[36] (2020)	China	Retrospective cohort	52	SARS-CoV-2	RT-PCR	120	No funding

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Chart 1. Main characteristics of the studies included in the review (n=36). (continuation)

Author, year of publication	Country	Study design	Age (mean years)	Coronavirus type	Diagnosis	Sample size	Funding sources
Habib et al.[71] (2019)	Saudi Arabia	Retrospective cohort	60 Standard deviation (SD) 18.2	MERS-CoV	RT-PCR	63	Sulaiman Al Rajhi Colleges, Saudi Arabia
Ho et al.[72] (2004)	China	Case report	36.5	SARS-CoV	Not informed	7	Not informed

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36).

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Antimalarial					
Chen J et al.[13] (2020)	A:hydroxychloroquine (HCQ) 400 milligrams (mg) per day for 5 days (n=15)	B: placebo (n=15)	Time to clinical improvement	Median of days	A: 1 (0-3) *versus* B: 1 (0-2)
			Detection of viral load by reverse transcription followed by polymerase chain reaction (RT-PCR)	% of negative	After 7 days: 86.7 versus 93.3 After 14 days: 100
			Radiological progression	% patients who improved	A: 33,0 *versus* B: 46,7
			Adverse events	Number of events	A: 4 (2 diarrheas, 1 worsening of the clinical picture with discontinuation of treatment, 1 transient increase in aspartate) versus B: 3 (1 increase in serum creatinine, 1 anemia, 1 transient increase in aspartate aminotransferase)
Chen Z et al.[14] (2020)	A: HCQ (400 mg/day 5 days (n=31)	B: standard treatment (oxygen therapy, antiviral agents, antibacterials and immunoglobulin, with or without corticosteroids) (n=31)	Time to clinical improvement	Mean days for normalizing body temperature Mean days for improving cough	A: 2.2 (standard deviation 0.4) versus B: 3.2, p=0.0008 A: 2 days (SD 0.2) versus B: 3.1 days, p=0.0016
			Radiological progression by computed tomography (CT)	% of pneumonia improvement	A: 80.6 versus B: 54.8, p=0.0476, Chi-square test
			Adverse events	Number of events	A: 2 (1 skin rash, 1 headache)

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Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Borba et al.[15] (2020)	A: high-dose chloroquine (CQ): 600mg/day for 10 days or total dose of 12 g (n=41) B: low-dose CQ: 450 mg for 5 days, twice a day only on the first day, or total dose of 2.7g (n=40)	No comparator	Mortality in 28 days	Mortality rate	A: 13.5%; 95% Confidence Interval 95% CI: 6.9-23.0
			Adverse events	% of patients who presented QT interval > 500ms	A: 11.1 versus B: 18.9
Tang et al.[16] (2020)	A: HCQ (200 mg/ day for three days followed by 800 mg/ day for 2 weeks for patients with mild symptoms and 3 weeks for severe symptoms (n=75)	B: standard treatment (standard care for COVID-19, according to the Chinese National Guide) (n=75)	Detection of viral load by RT-PCR	% of negative	A: 85,4 *versus* B: 81,3, p=0,341
			Time to negative viral load (RT-PCR)	Median days Relative Risk (RR)	A: 8 days versus B:7 days 0.846; 95% CI 0.58-1.23, p=0.341
			Clinical improvement	Median days Proportion of improvement	A: 19 days versus B: 21 days, p=0.96 A: 59.9; 95% CI 45.0-75.3 versus B: 66.6; 95% CI 39.5-90.9
			Adverse events	% de patients	Any adverse event - A: 30.0 versus B:8.8. p-value: 0.001 Most frequent adverse event (diarrhea): A: 10 versus B:0 Severe adverse event A:2.6 versus B: 0
Mahévas et al.[17](2020)	A: HCQ (600 mg/day started in the first 48h of hospitalization) (n=84) B: HCQ + azithromycin (AZT) (n=17) C: No exposure to HCQ (n=97)	No comparator	Transfer to Intensive Care Unit (ICU)	% of hospitalization RR	A: 20,2 *versus* B: 22,1 0,91 (0,48–1,81)
			Mortality by all causes	% of deaths RR	A: 2,8 *versus* B: 4,6 R0,61; IC 95%: 0,13–2,90
			Progression to severe acute respiratory syndrome (SARS)	% of patients RR	A: 9.5 These patients had to discontinue HCQ RR=1.15; 95% CI: 0.66–2.01
Magagnoli et al.[18] (2020)	A: HCQ (n=97) B: HCQ + AZT (n=113) Without HCQ (n=158)	No comparator	Mortality	% of deaths Adjusted RR	A: 27.8 versus B: 22.1 versus C:11.4 A: 2.61; 95% CI 1.10-6.17. P=0.03 versus B: 1.14; 95% CI 0.56-2.32. P=0.72
			Need for mechanical ventilation	% of patients Adjusted RR	A: 13.3 versus B: 6.9 versus C:14.1 A: 1.43; 95% CI 0.53 – 3.79. P=0.48 versus B: 0.43; 95% CI 0.16 -1.12; P=0.09

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Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Gautret et al.[19] (2020)	A: HCQ (600 mg/day for 10 days) (n=20) B: HCQ (600mg/day for 10 days) + AZT (500 mg/day for 4 days) (n=6) C: Standard treatment (n=16)	No comparator	Detection of viral load by RT-PCR	% of negative	After 6 days- A: 70.0 versus B: 12.5 Post-hoc analysis: A: 100.0 versus B: 57.1 versus C: 12.5. p<0.001
Chorin et al.[22] (2020)	A: HCQ+AZT (n=84)	No comparator	Adverse events	% of patients with alteration in the prolongation of the QT interval	>400ms: 30 > 500 ms: 11
Gautret et al.[21] (2020)	A: HCQ (200mg/day for 10 days) + AZT (500mg/day for 1 day, then 250 mg/day for 4 days)	No comparator	Negative viral load by RT-PCR	% of negative	A: 83 on day 7 and 93 on day 8
			Length of hospital stay	Median of days	A: 4.6
			Adverse events	% of events	A: 2.5 nausea and vomiting. 5 diarrheas. 1.2 blurry vision
Molina et al.[20] (2020)	A: HCQ (600 mg/day for 10 days) + AZT (500 mg/day on day 1 and 250 mg/day on days 2 to 5)	No comparator	Mortality	Number of deaths	A: 1
			Positive viral load by RT-PCR	% of positivity	80.0; 95% CI: 49–94
Antivirals and Antiretrovirals					
Li et al.[23] (2020)	A: Lopinavir (200 mg), by Ritonavir (50 mg) (administered orally, twice a day, 500 mg, each time for 7-14 days) (n=34) B: Arbidol (100 mg) (administered orally, 200 mg three times a day for 7-14 days) (n=35)	C: Without antiviral therapy (n=17)	Negative viral load by RT-PCR	% of negative	After 7 days: A: 35.3% versus B: 37.1% versus C: 41.2%. p=0.966 After 14 days: A: 85.3% versus B: 91.4% versus C: 76.5%. p=0.352
			Adverse events	Number of patients	A:12 (9 diarrheas. 1 elevation of alanine aminotransferase. 2 loss of appetite) versus B: 5 (3 diarrheas. 2 nauseas)
Young et al.[25] (2020)	A: Lopinavir/ ritonavir(n=5)	B: Without Lopinavir/Ritonavir	Clinical improvement	Body temperature normalization in days	A: 3 versus B: 3
				Time of use of supplemental oxygen therapy	A: -3 days
				Need for invasive mechanical ventilation	A: 2
			Adverse events	Number of events	A: 4 (Nausea, vomit, diarrhea, hepatic alterations)

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Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Cao et al.[24] (2020)	A: Lopinavir-Ritonavir 400 mg and 100 mg, administered orally, twice a day associated with standard treatment por 14 days (n=99)	B: standard treatment (n=100)	Time to clinical improvement	Length of stay in the Intensive Care Unit (number of days)	A: 6 versus 11
			Mortality	Mortality rate	19.2. 95% CI 17.3% to 5.7%
			Adverse events	Number of events	A: 19 (Gastrointestinal, including nausea, vomit and diarrhea) B: 32 (Respiratory failure. Acute kidney injury and secondary infection)
Immunomodulators					
Zhou et al.[26] (2020)	A: IFN-α2b nebulized (5mU, bid) n=7 B: INF + Arbidol (tablet – 200 mg, tid) n=46 C: Arbidol n=24	No comparator	Viral clearance	Median (interquartile range)	A: 8.0 (5.5-15.5) versus B: 6.5 (3.0-10.0) versus C: 10.0 (4.5-19.5)
Anticoagulant					
Negri et al.[27] (2020)	A: Heparin 1 mg/kg every 24hs	No comparator	Oxygenation index	PaO2/FiO2 ratio (standard deviation)	A: 325 (80). p=0.013
			Length of hospital stay	Mean (standard deviation)	A: 7.3 days (4.0)
			Length of mechanic ventilation	Mean (standard deviation)	A: 10.3 days (1.5)

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Antivirals and Antiretrovirals

Two clinical trials[23,24] and one case series[25] that reported treatments with lopinavir/ritonavir, arbidol (umifenovir), and interferon-α2b, were included. Most of the studies were conducted in China (n = 2), and all targeted SARS-CoV-2. One of the studies compared the use of lopinavir (associated with ritonavir) with arbidol (umifenovir) and standard treatment without antivirals[23]. The rate of negative SARS-CoV-2 viral load after seven days was 35.3% for the group that took lopinavir/ritonavir, 37.1% for the group that received arbidol, and 41.2% for the group that did not receive antiviral therapy[23]. Patients who received lopinavir/ritonavir associated with standard treatment had fewer days of hospitalization (6 days) than the group that received only standard treatment (11 days)[24]. Adverse events were also lower among the group that received the intervention (19 events in the intervention group versus 32 events in the control group)[24].

Immunomodulators

In a retrospective cohort[26] conducted in China, viral clearance took about eight days (IQR: 5.5-15.5) between the group that received nebulized interferon-α2b and 6.5 days (IQR: 3.0-10.0) for the group that received interferon associated with arbidol[26]. The group that received only arbidol took about 10 days (IQR: 4.5-19.5) for viral clearance[26].

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Shi C et al.[28] (2020)	A: Heparin (n=21)	Without heparin (n=21)	Length of hospital stay Viral clearance	Mean days (Interquartile range) Mean days (Interquartile range); p-value	A: - 29 days (7.0-42.0) versus B: 27 days (24.0-31.0) A:20;(11 -31) versus B:19;(12 - 30) P=0.46
			Coagulation parameters	Levels of D-dimer; standard deviation; p-value	A:(0.90±0.44.170 1.00±1.06. p=0.368) versus B:(3.75±4.04. 0.90±0.44. p=0.001)
			C-reactive protein levels	Levels of CRP; standard deviation; p-value	B:22.62±23.79. -20.23±33.91. p=0.660
			Inflammatory cytokine levels (IL6)	Levels of cytokines; standard deviation; p-value	A:47.47±58.86. 198 15.76±25.71. p=0.006) versus B: -32.46±65.97.200 14.96±151.09. p=0031
			Lymphocyte levels	Lymphocyte levels; standard deviation; p-value	A: 18.84±8.24. 29.94±7.92. p=0.00048 versus B:11.10±9.50. 3.08±9.66. p=0.011
Corticoids					
Arabi et al.[29] (2018)	A: Corticosteroids (n=151)	B: Without corticosteroids (n=158)	Mortality	Mortality rate	A: 74.2% B: 57.6% P= 0.002
			Need for invasive mechanical ventilation	% of days	A: 93.4 versus B: 76.6
Wang et al.[30] (2020)	A: Methylprednisolone, 1mg/(kg) for 5 to 7 days (n=26)	Without Methylprednisolone	Improvement of symptoms	Mean days and standard deviation	Body temperature normalization A: 2.06 (0.28) versus B: 5.29 (0.70). p=0.010 Need for higher supplemental oxygen therapy in the group without Methylprednisolone A: 8.2 (7.0) versus B: 13.5 (10.3) p<0.001

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Anticoagulants

Negri et al[27] evaluated the use of heparin for the treatment of COVID-19 in a hospital in São Paulo, Brazil. The PaO2/FiO2 oxygenation index was evaluated before and after 72 hours of treatment, besides the duration of hospitalization and mechanical ventilation. The PaO2/FiO2 ratio improved from 254 to 325 (p=0.013), the mean hospital stay was 7.3, and the mean duration of mechanical ventilation was 10.3[27]. Another study[28] evaluated heparin use in the

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Lu et al.[31] (2020)	A: Corticosteroids (n=31) Corticosteroids n=151 (hydrocortisone: 100-800mg/d) 8 (4-12) days (Methylprednisolone, dexamethasone and hydrocortisone) + oseltamivir, arbidol, lopinavir / ritonavir, ganciclovir, interferon-α)	B: without corticosteroids (n=31) Without corticosteroids n= 93 + oseltamivir, arbidol, lopinavir / ritonavir, ganciclovir, interferon-α)	Mortality in 28 days	Mortality rate OR;95% CI; p-value	A: 39% versus B: 16%. P=0.09 OR : 1.05; (-1.92-2.01); p-value = > 0.3
Auyeung et al.[32] (2005)	Corticoesteroids	Without corticosteroids	Mortality em 28 days	Odds Ratio	20.7 (1.3 – 338) – for admission in ICU* or death
Combined therapies					
Morra et al.[34] (2018)	A: INF alpha-2a, alpha-2b or beta-1a + ribavirin (n= 68)	B: Support measure (n=48)	Mortality em 28 days	Mortality rate	71% (61.8% - 79.5%) *Survival. Days (95% CI) A: 21.3 (14.1-28.5) B: 21.4 (12.4-30.4)
			Need for invasive mechanical ventilation	%	A: 76.0 versus B: 90.0
			Adverse events	Number of events	A: 3 (Elevation of pancreatic enzymes. Hemolysis.)
Al-Tawfiq e Memish[61] (2017)	A: ribavirin + IFN alfa2a B: ribavirin + IFN beta1a	Several comparators	Mortality in 28 days	Mortality rate	A: 85% B: 64%
Momattin et al.[62] (2013)	Ribavirin, lopinavir/ritonavir, convalescent plasma, INF alpha, corticosteroids	Several comparators	Mortality in 28 days	Mortality rate	4% (Lopinavir/ritonavir) From 6.5% to 12.7% (ribavirin) 12.5% (convalescent plasma) 23.8% (corticosteroid) 7.7% (corticosteroids) 0% (INFalpha-1)
			ICU admission rate	%	% a 20% (ribavirin) 23.1% (corticosteroids) 11.1% (INF alpha)

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treatment of COVID-19 through negative viral outcomes, coagulation parameters, the concentration of C-reactive protein and inflammatory cytokines, number of lymphocytes before and after treatment. There was no significant difference between the two groups, except for an increase in IL-6 and in lymphocytes in the intervention group. The authors pointed out that heparin im-

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Chiou et al.[35] (2005)	Oral ribavirin oral associated with Methylprednisolone, followed by oral prednisolone, Pulse methylprednisolone, oxygen therapy by nasal cannula, non-respiratory mask or mechanical ventilation (n=44)	Treatment without ribavirin (n=7)	Mortality in 28 days	Mortality rate	A: 29% B: 13%
			Absorption of infiltrations in the chest image	%	A: 71 versus B: 67. p=0.05)
			Level of hemoglobin (% of reduction)	%	A: 73 versus B: 14. p=0.006
Lau et al.[63] (2004)	Intravenous ribavirin (3,3 mg/kg of body weight) Corticosteroids (Methylprednisolone 0,3 mg/kg for 10 days, oral prednisolone at 1 mg/kg (n=71) +	No comparator	Mortality in 28 days	Mortality rate	3.4%
			Time to clinical stabilization	Mean	8 days
			Adverse events	% of events	Hyperglycemia (58%). Pneumothorax (13%). Psychiatric manifestations (7%). Pneumonia associated with mechanical ventilation (2%)
Chen X et al.[64] (2020)	ICU care Oxygen therapy Mechanical ventilation Antibiotics Ribavirin Chloroquine Corticosteroid Immunoglobulin Oseltamivir lopinavir/ritonavir Arbidol (n = 185;viral clearance ≤14 days)	ICU care Oxygen therapy Mechanical ventilation Antibiotics Ribavirin Chloroquine Corticosteroid Immunoglobulin Oseltamivir lopinavir/ritonavir, arbidol (n = 95 viral clearance >14 days)	Hospital discharge with cure	Number of cases	A:183 versus B:91
			Hospital stay	Number of cases	A:0 versus B:3
			Death	Number of cases	A:1 versus B:0
			Hospital stay in days	Number of days; IQR; p-value	A:17(12-23) versus B:21 (15 -28)
			Hospital admission time to viral Clearance in days	p-value=<0.000	A: 5 (3 -8) versus B:14 (9 -19) p-value = <0.0001

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proves coagulation dysfunction, has anti-inflammatory effects, and can be used as a treatment for COVID-19[28].

Corticoids

Four retrospective cohorts[29-32] reported corticosteroid therapies. Two were performed in China, focusing on the SARS-CoV-2[30,31] coronavirus. The time to symptom improvement was assessed and was shorter in the group that received methylprednisolone (2.06 days) than in the group that did not receive treatment (5.29 days)[30]. One study showed a higher mortality rate for patients with COVID-19 who received corticosteroids (39%) than in the group of patients who did not receive them (16%; p = 0.09)[31]. In patients with MERS-CoV, the mortality rate (74.2% versus 57.6%) and the need for invasive mechanical ventilation (93.4% versus 76.6%) were higher in the group receiving corticosteroids than in the group control group[29]. SARS-CoV patients who received corticosteroids were 20.7 times more likely (OR = 20.7; 95% CI: 1.3-338) to be admitted to the ICU or die than those who did not use corticosteroids[32].

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36).

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Bian et al.[33] (2020)	Meplazumab (10 mg on the 1st, 2nd and 5th day via intravenous infusion within 60 to 90 minutes) + Lopinavir/ritonavir Interferon α-2b Glucocorticoid Antibiotic (n=17)	Lopinavir/ritonavir Interferon α-2b Glucocorticoid Antibiotic (n=11)	Hospital discharge (28th day)	Number of cases; p-value	A:16 versus B:9 P=0.006.
			Improving chest X-rays (7th, 14th and 21st day post-treatment)	P-value	p=0.010; 0.006;0.037
			Viral clearance	Median of days; IQR	A:3(1.5 - 4.5) versus A:0.37 (0.155 - 0.833); p-value 0.014
			Increased C-reactive protein concentration in 28 days	HR; P-value	A:14; p-value = <0.05
			Elevation of ALT and AST	Number of cases; p-value	A:2 B:2
Shi Q et al.[65] (2020)	Antiviral Antibiotics Glucocorticoid Immunoglobulin High-flow oxygen inhalation Non-invasive mechanical ventilation Invasive mechanical ventilation Continuous renal replacement therapy (n=101)	No comparator	Mortality up to 3 days	Number of cases	48
			Mortality after 3 days	Number of cases	53

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Combined therapies

Bian et al.[33] evaluated the efficacy of meplazumab, an anti-CD147 antibody, as a complementary therapy in patients with COVID-19 in China. Other associated treatments were antiretroviral (lopinavir/ritonavir), immunomodulator (recombinant interferon α-2b), glucocorticoid, and antibiotic (not specified) drugs. The control group did not receive meplazumab. In the intervention group, 94% of patients (p = 0.006) were discharged from the hospital, and the median for the negative viral load was three days, with an increased C-reactive protein in 82.4% of cases. The reported adverse effects were only 2 cases that had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and the condition was reversed after seven days. The researchers reported that this increase in transaminases was not associated with the use of meplazumab, as the same effect was observed in the control group[33].

In another study[31], treatment with corticosteroids (methylprednisolone, dexamethasone, and hydrocortisone) associated with antivirals (oseltamivir, arbidol, ganciclovir, interferon-α) and antiretrovirals (lopinavir/ritonavir) was compared with a group that received the same treatment, without corticosteroids. No difference was observed between the groups (adjusted OR = 1.05; 95% CI: -1.92 to 2.01, p > 0.3)[31] in the mortality outcome after 28 days of hospitalization.

In yet another study[34], treatment with interferon associated with ribavirin was evaluated, compared with the use of a support measure for the treatment of MERS. There was a need for

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Jiang et al.[66] (2020)	Antiviral: Interferon α Lopinavir/ritonavir Arbidol Chloroquine Antibiotic Antifungal Corticosteroid Immunoglobulin Timosine Probiotics Low molecular weight heparin High-flow oxygen cannula Mechanical ventilation Transfusion of convalescent plasma Extracorporeal membrane oxygenation Lung transplant (n=47; non-severe cases)	Antiviral: Interferon α Lopinavir/ritonavir Arbidol Chloroquine Antibiotic Antifungal Corticosteroid Immunoglobulin Timosine Probiotics Low molecular weight heparin High-flow oxygen cannula Mechanical ventilation Transfusion of convalescent plasma Extracorporeal membrane oxygenation Lung transplant (n=8; severe cases)	Liver damage	Number of cases; p-value	A:12 (25.5%) versus B:4 (50%) P=0.0323
			Acute respiratory syndrome	Number of cases; p-value	A:2 (4.3%) versus B:2 (25%) p-value= 0.073
			Respiratory arrest	Number of cases; p-value	A:2(4,3%) versus B:8 (100%) P valor=<0,00
			Secondary infection	Number of cases; p-value	A:2(4.3%) versus B:8 (100%) p-value=<0.00
			Acute kidney injury	Number of cases; p-value	A:2(4.3%) versus B:2(25%) p-value = 0.176 A:1(2.1%) versus B:2 (25%) p-value = 0.073
Hu et al.[67] (2020)	Antiviral: Oseltamivir Ganciclovir Arbidol Kaletra Interferon -α Antibiotics: moxifloxacin Corticosteroid/ Glucocorticoid Continuous renal replacement Alternative therapy: Non-invasive ventilation Invasive ventilation (n=260; favorable clinical outcome)	Antiviral: Oseltamivir Ganciclovir Arbidol Kaletra Interferon -α Antibiotics: moxifloxacin Corticosteroid/ Glucocorticoid Continuous renal replacement Alternative therapy: Non-invasive ventilation Invasive ventilation (n=63; unfavorable clinical outcome)	Shock	Number of events; p-value	A:8 versus B:35 p-value = <0.001
			Acute cardiac injury	Number of events; p-value	A:3 versus B:21 p-value = <0.001
			Arrhythmia	Number of events; p-value	A:51 versus B:47 p-value = <0.001
			Acute respiratory syndrome grave	Number of events; p-value	A:56 versus B:44 p-value = <0.001
			Acute kidney injury	Number of events; p-value	A:3 versus B:14 p-value = <0.001
			Acute lung injury	Number of events; p-value	A:56 versus B:44 p-value = <0.001
			Septic shock	Number of events; p-value	A:0 versus B:19 p-value = <0.001
			Secondary infection	Number of events; p-value	A:0 versus B:9 p-value = <0.001

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mechanical ventilation in 76% of patients in the intervention group compared with 90% in the control group. The adverse effects reported in the intervention group were elevation of pancreatic enzymes and hemolysis, present in 3 patients[34].

Chiou et al.[35] evaluated a therapy with an antiviral (ribavirin) associated with corticosteroids (methylprednisolone, prednisone) for the treatment of COVID-19 compared with a regimen without ribavirin. An improvement in the chest

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Duan et al.[68] (2020)	Convalescent plasma 200Ml + Ribavirin 0,5g, Arbidol 0,2g, Remdesivir 0,2g, Interferon-α 500MIU, Oseltamivir, Peramivir (n=10)	Ribavirin, Arbidol, Remdesivir Interferon-α, Cefoperazone Moxifloxacin Methylprednisolone (N=10) ** Control group results were not shown in the studies	Titer of neutralizing antibodies after treatment with PC	Titers; Number of cases	A:1:640;10
			Clinical improvement of symptoms; fever, cough, shortness of breath, chest pain	Mean days	A:3
			Improvement of symptoms of chest X-rays	Mean days	A:7
			Viral clearance	Number of cases	A:10
			Adverse effects red spots on the face	Number of cases	A:2
Chen H et al.[69] (2020)	Danoprevir 100 mg twice a day + Ritonavir 100 mg twice a day with or without nebulization of Interferon 5 uM, 4 to 12 days (n=9, who had already received antivirals)	Danoprevir Ritonavir Nebulization with Interferon (n=2, diagnosed recently and not having received antivirals)	Hospital discharge	Number of cases; number of days	A:9;4 to 12 versus A:2;4 to 12
			Normal body temperature for at least 3 days	Number of cases; number of days	A:9;4 to 12 versus A:2;4 to 12
			Significant recovery from respiratory symptoms	Number of cases; number of days	A:9;4 to 12 versus A:2;4 to 12
			Improved chest images	Number of cases; number of days	A:9;4 to12 versus A:2;4 to 12
			Two consecutive negative RT-PCR tests	Number of cases; number of days	A:9;4 to 12 versus A:2;4 to 12
			Length of hospital stay	Median of days; number of days	A:20 (7-22) versus B: 9.7
Tsui et al.[70] (2003)	Antibiotics (levofloxacin, amoxicillin/ clavulanate) + combination of ribavirin and steroids (n=323)	No comparator	Mortality	Mortality rate	7.9% (5-10.8%)
		Without lopinavir/ Ritonavir Corticosteroid Antibiotics Oxygen therapy with nasal cannula Non-invasive mechanical ventilation Invasive mechanical ventilation (n=42)	Need for invasive mechanical ventilation	%	13%

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image's infiltrations was reported by 71% of the patients who received ribavirin compared to the control group (67%, p = 0.05)[35].

A study[36] compared the use of antiretrovirals (lopinavir/ritonavir), corticosteroids, antibiotics, and supportive treatment vis-à-vis a similar treatment, but without lopinavir/ritonavir. The time to viral clearance had a median of 22 days compared to 28.5 in the control group. Moreover, the median hospital stay was 23 days compared to 18.5 in the control group[36].

Chart 2. Effects of drug treatments against human Coronavirus infection (n = 36). (continuation)

Studies (year)	Intervention	Comparator	Outcomes	Measure of effect	Result
Yan et al.[36] (2020)	Lopinavir/Ritonavir (400 mg and 100 mg, orally, twice a day) + Corticosteroid Antibiotics Oxygen therapy com nasal cannula Non-invasive mechanical ventilation Invasive mechanical ventilation (n=78)		Without lopinavir/ Ritonavir Corticosteroid Antibiotics Oxygen therapy with nasal cannula Non-invasive mechanical ventilation Invasive mechanical ventilation (n=42)	Days of treatment Median of days; IQR	A:22 (18-29) versus B:28.5 (19.5 - 38)
				Viral clearance Median of days; IQR	A:22 (18-29) versus B:28.5 (19.5 - 38)
				Hospital stay Median of days; IQR	A:23 (19-27) versus B:18.5 (13 -22.5)
Habib et al.[71] (2019)	A: Ribavirin + Interferon (IFN) (n=63)	No comparator	Mortality	Mortality rate	A: 22.9%
Ho et al.[72] (2004)	Post-treatment pentaglobin with corticosteroids and ribavirin	No comparator	Absorption of infiltrations in the chest image Improvement between days 1, 5 and 7	Median and IQR	5 liters (L); 8–12 L (day 1) 7.5L; 5–9.5 L (day 5) 6L; 2.5–8 L (day 7)
			Need for oxygen	Median and IQR	Improvement between days 1, 6 and 7 2.5 L/min*; 2–4 L/min (day 1) 1 L/min; 0–2.8 L/min (day 6) 0.5 L/min; 0–2.8 L/min (day 7)

CK: creatine phosphokinase; CQ: chloroquine; SD: standard deviation; HCQ: hydroxychloroquine; OR: Odds Ratio; PaO2/FiO2: Oxygenation index; NA: not applicable; IQR: interquartile range, CT: computed tomography; ICU: Intensive Care Unit.

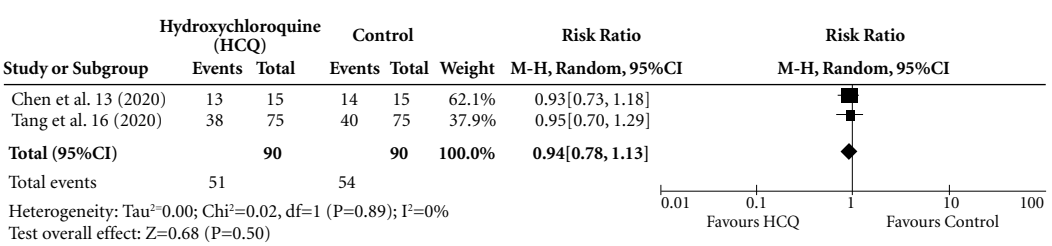

Figure 2. Negative viral load by recal-time polymerase chain reaction (RT-PCR) after seven days of treatment with hydroxychloroquine.

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Methodological quality assessment

In general, the methodological quality of the included studies was moderate. The main limitations of the included randomized clinical trials were lack of allocation secrecy, blinding, and sample size of fewer than 100 participants. The primary limitations observed in the systematic reviews were related to the authors' clarity regarding the process of assessing the risk of bias in the included studies, lack of description of eligibility criteria, and discussion about the heterogeneity in the findings. The included cohort studies were unclear as to the information about the control of confounding variables, length of follow-up, and patient eligibility criteria, besides the lack of comparable groups. Case series did not adequately describe patient eligibility criteria, demographic characteristics, and clinical data. No study was excluded because of its methodological quality. The critical assessment of the individual quality of each study is found in Charts 3-6.

Discussion

This review identified three systematic reviews, eight randomized clinical trials, 18 cohorts, and seven case series, evaluating different drug alternatives to human coronavirus, who reported mortality in 14 days, a progression of lung lesions on computed tomography, clinical improvement, absence of viral detection in RT-PCR and adverse events. Antivirals and antimalarials were among the most studied therapies.

When there are no clinically proven treatments during epidemics, the tendency is to use drugs based on *in vitro* activity or observational studies. However, effective drugs based on *in vitro* studies and observational studies for other diseases were later proven to be ineffective in clinical trials[37].

CQ and HCQ showed *in vitro* inhibitory effects on coronavirus infections[38,39]. As a known antimalarial and anti-autoimmune agent, HCQ appears to block infection by the SARS-CoV virus, increasing the endosomal pH required for membrane fusion between the virus and the host cell[40,41].

Furthermore, it has been shown to specifically inhibit SARS-CoV-2 replication by interfering with the glycosylation of the angiotensin-converting enzyme 2 (ACE2)[42]. *In vitro* tests have revealed its ability to reduce the number of viral copies of SARS-CoV-2[43] effectively.

Considering the low costs of CQ, good safety profile, *in vitro* activity against other viruses[44,45], pre-existing supply chain with potential for increased public and private production, and knowledge about specificity and management of accumulated side effects of use in malaria, some countries have recommended the use of CQ in the treatment of COVID-19. In China, CQ was added to the COVID-19 guideline for prevention, control, diagnosis, and management on February 18, 2020[46]. In the U.S., the Food and Drug Administration issued an emergency use authorization for CQ/HCQ to treat this disease on March 28, 2020[47]. The European Drug Agency claimed that the two drugs should be used in clinical trials or national drug programs of emergency use for the treatment of COVID-19 on April 1st, 2020[48].

Clinical trials are underway in several countries to evaluate the use of chloroquine or hydroxychloroquine for COVID-19. The best available evidence, until April 2020, failed to demonstrate or exclude a beneficial effect of CQ or HCQ on human coronavirus infections or viral negative by RT-PCR[13-19,22]. Furthermore, the results presented are limited and should be interpreted with caution since the essential outcomes for patients (e.g., mortality, rate of progression of the severe acute respiratory syndrome, and need for mechanical ventilation) were not reported in most publications.

Patients have been receiving off-label and compassionate therapies[37], and the association of lopinavir and ritonavir stood out among the treatments tested for COVID-19[49]. These drugs are used in combination to increase plasma half-life by inhibiting cytochrome P450[24]. Some have raised the hypothesis that lopinavir/ritonavir inhibits protease in a similar way to SARS and MERS 3-chymotrypsin and appears to be associated with better clinical outcomes in patients with SARS[50]. This inhibitor, which was used mainly for HIV infection, has activity *in vitro* against SARS-CoV[51] and appears to have some activity against MERS-CoV in animal studies[52]. Evidence for the use of lopinavir/ritonavir is still limited for SARS-CoV-2, and further studies should be conducted to determine the efficacy and safety of these drugs[49].

The use of corticosteroids for viral pneumonia still has inconclusive effects among studies, and so far, it is difficult to have a position on the use of corticosteroids in patients with SARS-CoV-2[26]. A diagnosis and treatment regimen was published by the National Health Commission of China, where corticosteroid therapy was indicat-

Chart 3. Evaluation of the methodological quality of the included cohort studies (n = 18).

Author, year of publication	Items											#yes
	1	2	3	4	5	6	7	8	9	10	11	
Wang et al.[30] (2020)	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	8/11
Habib et al.[71] (2019)	N	Y	Y	Y	Y	Y	Y	Y	NC	N	Y	8/11
Arabi et al.[29] (2018)	Y	Y	Y	Y	Y	Y	Y	Y	NC	Y	Y	10/11
Auyeung et al.[32] (2005)	NC	Y	Y	Y	Y	Y	Y	NC	NC	NC	Y	7/11
Chiou et al.[35] (2005)	N	Y	Y	NC	N	Y	Y	Y	Y	NC	Y	7/11
Lau et al.[63] (2004)	NC	Y	Y	N	N	Y	Y	Y	N	N	Y	6/11
Tsui et al.[70] (2003)	Y	NC	NC	Y	Y	Y	Y	Y	Y	N	Y	8/11
Gautret et al.[19] (2020)	N	NC	N	N	N	Y	Y	NC	Y	NC	Y	4/11
Shi Q et al.[65] (2020)	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	9/11
Zhou et al.[26] (2020)	Y	N	N	N	N	Y	Y	Y	Y	N	Y	9/11
Mahévas et al.[17] (2020)	N	Y	Y	N	N	Y	Y	Y	Y	NC	Y	7/11
Magagnoli et al.[18] (2020)	N	Y	Y	Y	Y	Y	Y	N	Y	NC	Y	8/11
Lu et al.[31] (2020)	Y	Y	Y	Y	N	Y	Y	N	N	N	Y	7/11
Yan et al.[36] (2020)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	9/11
Chen X et al.[64] (2020)	Y	Y	Y	NC	Y	Y	Y	Y	Y	NC	Y	9/11
Jiang et al.[66] (2020)	Y	Y	Y	N	N	Y	Y	Y	Y	NC	Y	8/11
Hu et al.[67] (2020)	Y	Y	Y	N	N	Y	Y	Y	Y	NC	Y	8/11
Shi C et al.[28] (2020)	S	S	S	N	N	S	S	S	S	NA	S	8/11

Y: Yes; N: No; NC: Not Clear; #Yes: number of "yes"; Items: 1. Were the two groups similar and recruited from the same population? 2. Were exposures similarly measured to assign people to exposed and unexposed groups? 3. Was the exposure measured in a valid and reliable manner? 4. Have confounding factors been identified? 5. Have strategies for addressing confounding factors been stated? 6. Were the participants free of the result at the beginning of the study (or at the time of exposure)? 7. Were the results measured in a valid and reliable way? 8. Was the follow-up time reported and sufficient to be long enough for the results to occur? 9. Was the follow-up complete and, if not, were the reasons for the loss described and explored? 10. Were strategies used to deal with incomplete follow-up? 11. Was an appropriate statistical analysis used?

Chart 4. Evaluation of the methodological quality of the included systematic reviews (n = 3).

Author, year of publication	AMSTAR items																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall confidence in the results
Morra et al.[34] (2018)	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N	Low
Al-Tawfiq and Memish[61] (2017)	Y	Y	N	Y	Y	N	N	N	N	Y	NA	NA	N	N	N	Y	Critically low
Momattin et al.[62] (2013)	Y	Y	N	N	Y	N	N	N	N	Y	N	N	N	N	N	Y	Critically low

N: No; NA: Not Applicable; Y: Yes; #Yes: Number of "yes"; AMSTAR items: 1. Do the research questions and inclusion criteria for the review include the PICO components? 2. Did the review report contain an explicit statement that the review methods were established before the review and did it justify any significant deviation from the protocol? 3. Did the review authors explain their selection of study designs for inclusion in the review? 4. Did the review authors use a comprehensive literature search strategy? 5. Did the review authors select the study at least in independent pairs? 6. Did the review authors extract duplicate data? 7. Did the review authors provide a list of excluded studies and justify the exclusions? 8. Did the review authors describe the included studies in adequate detail? 9. Did the review authors use a satisfactory technique to assess the risk of bias in individual studies that were included in the review? 10. Did the review authors report sources of funding for the studies included in the review? 11. If a meta-analysis was performed, did the review authors use appropriate methods to statistically combine the results? 12. If the meta-analysis was performed, did the review authors assess the potential impact of the risk of bias in individual studies on the results of the meta-analysis? 13. Did the review authors explain the risk of bias in primary studies when discussing the results of the review? 14. Did the review authors provide a satisfactory explanation and discuss any heterogeneity observed in the review results? 15. If they performed a quantitative synthesis, did the review authors conduct an adequate investigation of the publication bias and discuss its likely impact on the results of the review? 16. Did the review authors report any potential sources of conflict of interest?

Chart 5. Evaluation of the methodological quality of the included case series (n = 7).

Author, year of publication	Items										#Yes
	1	2	3	4	5	6	7	8	9	10	
Chorin et al.[22] (2020)	N	Y	I	Y	Y	N	Y	I	N	Y	5/10
Molina et al.[20] (2020)	N	N	I	Y	I	N	Y	N	N	Y	3/10
Gautret et al.[21] (2020)	Y	Y	Y	Y	Y	N	Y	I	N	Y	7/10
Young et al.[25] (2020)	Y	Y	Y	N	Y	N	Y	Y	Y	NA	7/10
Ho et al.[72] (2004)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Negri et al.[27] (2020)	Y	N	Y	N	Y	N	Y	Y	Y	NA	6/10
Duan et al.[68] (2020)	Y	Y	Y	NC	NC	Y	Y	Y	Y	Y	8/10

N: No; Y: Yes; NA: Not Applicable; NC: Not Clear; #Yes: number of "yes"; I: Items: 1. Were there clearly defined inclusion criteria? 2. Was the condition measured in a standardized and reliable way for all participants? 3. Were valid methods used to identify the condition in the included participants? 4. Did the case series have consecutive inclusion of participants? 5. Did the case series have a full inclusion of participants? 6. Was there a clear account of the participants' demographic characteristics? 7. Was there a clear report of the participants' clinical information? 8. Were the outcomes or results of follow-up clearly reported? 9. Was there a clear report of the demographic information of the places or clinics? 10. Was there appropriate statistical analysis?

Chart 6. Evaluation of the methodological quality of the included clinical trials (n = 8).

Study	Randomization	Allocation secrecy	Blinding	Incomplete outcomes	Selective report	Other bias sources
Borba et al.[15] (2020)	+	+	-	?	+	+
Tang et al.[16] (2020)	+	-	-	+	+	-
Li et al.[23] (2020)	?	+	+	+	-	+
Chen J et al.[13] (2020)	-	-	-	+	+	-
Chen Z et al.[14] (2020)	+	?	?	+	-	+
Cao et al.[24] (2020)	+	?	?	+	-	+
Chen H et al.[69] (2020)	-	-	-	+	+	-
Bian et al.[33] (2020)	-	-	-	+	+	-

+: Low bias risk; -: High bias risk; ?: Unquantifiable risk.

ed as adjuvant therapy, as its use was associated with a delayed viral clearance[53]. A meta-analysis identified that patients with severe conditions were more likely to require corticosteroid therapy and to have a higher mortality rate and adverse effects[54]. According to the Centers for Disease Control and Prevention (CDC)[55], the use of corticosteroids cannot be indicated based on observational data. Both the CDC and the WHO believe that the use of corticosteroids should only be indicated when there is septic shock, asthma exacerbation, or chronic obstructive pulmonary disease[55,56]. Thus, the use of corticosteroids remains controversial[57].

In total, 202 studies investigating different alternatives for the treatment of COVID-19 are in progress (Chart 7).

Most of them are being developed in China, are not yet recruiting participants, are expected to end in 2020, and are available on the ClinicalTrials.gov and Chinese Clinical Trial Registry platforms. Ongoing trials vary in the study's design, the severity of the disease in the target population, the dosage, and the duration of treatment. The WHO[58] published guidelines on the ethics of testing amid outbreaks in 2016 and is working to standardize the design of the studies.

The number of studies conducted in parallel suggests that the scientific community is making a great effort to search for safe and effective treatments. However, there is a high likelihood that we are dealing with a virtually untreatable disease, only in need of supportive measures[59]. Besides the financial resources involved with unproven

Chart 7. Clinical trials registered for the management of COVID-19 (n = 202).

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
Platelet antiaggregants					
NCT04344756 France	Tinzaparin or unfractionated heparin	Standard treatment	Phase 2, Not yet recruiting	14/04/2020	Assistance Publique - Hôpitaux de Paris
NCT04352400 Italy	Nafamostat Mesylate	Placebo	Phase 2 and 3, Not yet recruiting	20/04/2020	University Hospital of Padua
NCT04345848 Switzerland	Enoxaparin	Prophylactic anticoagulation	Phase 3, Not yet recruiting	15/04/2020	University Hospital, Geneva
Monoclonal antibodies					
NCT04344782 France	Bevacizumab injection	Service standard	Phase 2, Not yet recruiting	14/04/2020	Assistance Publique – Hôpitaux de Paris
NCT04348500 United States	Clazakizumab	Placebo	Phase 2, Not yet recruiting	16/04/2020	Medical Center Cedars-Sinai
NCT04346797 France	Eculizumab	Service standard	Phase 2, Not yet recruiting	15/04/2020	Assistance Publique – Hôpitaux de Paris
NCT04335071 Switzerland	Tocilizumab	Placebo	Phase 2, Recruiting	06/04/2020	University Hospital Inselspital, Bern
NCT04335305 Spain	Tocilizumab	Standard treatment	Phase 2, Recruiting	06/04/2020	MedSIR
NCT04315480 Italy	Tocilizumab	No information	Phase 2, Not yet recruiting	19/03/2020	Università Politecnica delle Marche
NCT04322188 Italy	Siltuximab	Standard treatment without siltuximab	Recruitment	26/03/2020	AO Ospedale Papa Giovanni XXIII
NCT04343651 United States	Leronlimab (700mg)	Placebo	Phase 2, Recruitment	13/04/2020	CytoDyn, Inc.
NCT04347239 United States	Leronlimab (700mg)	Placebo	Phase 2, Recruitment	15/04/2020	CytoDyn, Inc.
NCT04346355 Italy	Tocilizumab	Service standard	Phase 2, Recruitment	15/04/2020	Azienda Unità Sanitaria Locale Reggio Emilia
NCT04329650 Spain	Siltuximab	Methylprednisolone	Phase 2, Recruitment	01/04/2020	Judit Pich Martínez
NCT04320615 United States	Tocilizumab	Placebo	Phase 3, Recruitment	25/03/2020	Hoffmann-La Roche
NCT04341116 United States	TJ003234	Placebo	Phase 1 and 2, Recruitment	10/04/2020	I-Mab Biopharma Co., Ltd.
NCT04351152 United States	Lenzilumab	Standard treatment	Phase 3, Not yet recruiting	17/04/2020	Humanigen, Inc.
NCT04345445 Malaysia	Tocilizumab	Methylprednisolone	Phase 3, Not yet recruiting	14/04/2020	University of Malaysia
NCT04332913 Italy	Tocilizumab	No information	Recruitment	03/04/2020	University of Áquila
NCT04317092 Multicenter	Tocilizumab	No comparator	Phase 2, Recruiting	20/03/2020	National Cancer Institute, Naples
NCT04342897 United States	LY3127804	Placebo	Phase 2, Recruitment	13/04/2020	Eli Lilly and Company
NCT04346199 Spain	Acalabrutinib	Standard treatment	Phase 2, Not yet recruiting	15/04/2020	AstraZeneca
NCT04331795 United States	Tocilizumab	No comparator	Phase 2, Recruiting	02/04/2020	University of Chicago
NCT04336410 United States	Tocilizumab	Standard treatment	Phase 2, Recruiting	26/03/2020	Marius Henriksen

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04331808 France	Tocilizumab	Standard treatment	Phase 2, Not yet recruiting	02/04/2020	Assistance Publique – Hôpitaux de Paris
NCT04343989 United States	Clazakizumab	Placebo	Phase 2, Recruiting	14/04/2020	NYU Langone Health
NCT04327388 United States	Sarilumab	Placebo	Phase 2 and 3, Recruitment	31/03/2020	Sanofi
NCT04324073 France	Sarilumab	Standard treatment	Phase 2 and 3, Not yet recruiting	27/03/2020	Assistance Publique - Hôpitaux de Paris
Anti-inflammatory drugs					
NCT04350320 Spain	Colchicine	Standard treatment	Phase 3, Not yet recruiting	17/04/2020	Foundation for Health Training and Research in the Region of Murcia
NCT04326790 Greece	Colchicine	Standard treatment	Phase 2, Not yet recruiting	30/03/2020	National and Kapodistrian University of Athens
NCT04328480 Argentina	Colchicine	Standard treatment	Phase 3, Not yet recruiting	31/03/2020	Estudios Clínicos Latino América
NCT04322565 Italy	Colchicine	Standard treatment	Phase 2, Not yet recruiting	26/03/2020	Azienda Ospedaliero-Universitaria di Parma
NCT04338958 Germany	Ruxolitinib	No comparator	Phase 2, Not yet recruiting	08/04/2020	University of Jena
NCT04331665 Canada	Ruxolitinib	No information	Not yet recruiting	02/04/2020	University Health Network, Toronto
NCT04332042 Italy	Tofacitinib	No information	Phase 2, Not yet recruiting	02/04/2020	Università Politecnica delle Marche
NCT04325061 Spain	Dexamethasone	Standard treatment	Phase 4, Recruitment	27/03/2020	University Hospital Dr. Negrin
NCT04325633 France	Naproxen	Standard treatment	Phase 3, Not yet recruiting	27/03/2020	Assistance Publique - Hôpitaux de Paris
NCT04333472 Israel	Piclidenoson	Standard treatment	Phase 2, Not yet recruiting	03/04/2020	BioPharma Can-Fite
NCT04321096 Denmark	Camostat Mesylate	Placebo	Phase 1, Recruitment	25/03/2020	University of Aarhus
NCT04353284 United States	Camostat Mesylate	Placebo	Phase 2, Not yet recruiting	20/04/2020	Yale University
NCT04323592 Italy	Methylprednisolone	Standard treatment	Phase 2 and 3, Recruitment	26/03/2020	University of Trieste
NCT04334629 United Kigdom	Ibuprofen	Standard treatment	Phase 4, Not yet recruiting	06/04/2020	King's College London
NCT04341584 France	Anakinra	Standard treatment	Phase 2, Not yet recruiting	10/04/2020	Assistance Publique - Hôpitaux de Paris
Antimalarials					
NCT04331600 Poland	Chloroquine	Standard treatment	Phase 4, Not yet recruiting	02/04/2020	Wroclaw Medical University
NCT04328493 Vietnam	Chloroquine	No intervention	Phase 2, Recruitment	31/03/2020	Clinical Research Unit of the University of Oxford, Vietnam
NCT04353336 Egypt	Chloroquine	No intervention	Phase 2 and 3, Not yet recruiting	20/04/2020	University of Tanta

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04342650 Brazil	Chloroquine	Placebo	Phase 2, Recruitment	13/04/2020	Dr. Heitor Vieira Dourado Tropical Medicine Foundation
NCT04328272 Pakistan	Hydroxychloroquine	Active comparator: Azithromicyn and placebo: Sugar Tablets	Phase 3, Not yet recruiting	31/03/2020	Faculty of Medicine of Ayub, Abbottabad
NCT04328467 United States	Hydroxychloroquine	Placebo	Phase 3, Recruitment	31/03/2020	University of Minnesota
NCT04353271 United States	Hydroxychloroquine	Placebo	Phase 2 and 3, Recruitment	20/04/2020	University of South Alabama
NCT04346667 Paquistan	Hydroxychloroquine	Placebo	Phase 4, Not yet recruiting	15/04/2020	Government of Punjab, Health and Specialized Medical Education Department
NCT04350450 United States	Hydroxychloroquine	No intervention	Phase 2, Not yet recruiting	17/04/2020	Montefiore Medical Center
NCT04334967 United States	Hydroxychloroquine	Standard treatment and Vitamin C	Phase 4, Registration through invitation	06/04/2020	Providence Health and Services
NCT04332991 United States	Hydroxychloroquine	Placebo	Phase 3, Recruitment	03/04/2020	Massachusetts General Hospital
NCT04342169 United States	Hydroxychloroquine	Placebo	Phase 2, Recruitment	10/04/2020	University of Utah
NCT04342221 Germany	Hydroxychloroquine	Placebo	Phase 3, Recruitment	10/04/2020	University Hospital of Tuebingen
NCT04315896 Mexico	Hydroxychloroquine	Placebo	Phase 3, Recruitment	20/03/2020	National Institute of Respiratory Diseases, Mexico
NCT04329611 Canada	Hydroxychloroquine	Placebo	Phase 3, Recruiting	01/04/2020	Dr. Michael Hill; Alberta Health Services; University of Alberta; University of Calgary; Calgary Health Trust; Alberta Innovates Health Solutions; Government of Alberta
NCT04342156 Singapore	Hydroxychloroquine	No intervention	Phase 3, Not yet recruiting	10/04/2020	Hospital Tan Tock Seng
NCT04340544 Germany	Hydroxychloroquine	Placebo	Phase 3, Not yet recruiting	09/04/2020	University Hospital of Tuebingen
NCT04333628 Israel	Chloroquine	Standard treatment	Phase 2 and 3, Not yet recruiting	03/04/2020	HaEmek Medical Center, Israel
NCT04323527 Brazil	Chloroquine	High-dose chloroquine (10 days)	Phase 2, Recruiting	26/03/2020	Dr. Heitor Vieira Dourado Tropical Medicine Foundation
NCT04351620 United States	Hydroxychloroquine	No comparator	Phase 1, Recruiting	17/04/2020	University of Chicago
NCT04334382 United States	Hydroxychloroquine	Azithromicyn	Phase 3, Recruiting	06/04/2020	Intermountain Health Care, Inc.
NCT04345692 United States	Hydroxychloroquine	Standard treatment	Phase 3, Recruiting	14/04/2020	Queen's Medical Centre

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04323631 Israel	Hydroxychloroquine	No comparator	Phase 1, Not yet recruiting	26/03/2020	Rambam Health Care Campus
NCT04351516 Germany	Hydroxychloroquine	Placebo	Phase 2 and 3, Recruiting	17/04/2020	University Hospital of Tuebingen
NCT04333654 United States	Hydroxychloroquine	Placebo	Phase 1, Recruiting	03/04/2020	Sanofi
NCT04325893 France	Hydroxychloroquine	Placebo	Phase 3, Recruiting	30/03/2020	University Hospital, Angers
NCT04316377 Norway	Hydroxychloroquine	Standard treatment	Phase 4, Recruiting	20/03/2020	University Hospital of Akershus
Antivirals and antiretrovirals					
NCT04334460 United States	BLD-2660	Placebo	Phase 2, Not yet recruiting	06/04/2020	Therapeutics of the lamina
NCT04333589 China	Favipiravir	Standard treatment	Recruitment	03/04/2020	Peking University First Hospital
NCT04346628V United States	Favipiravir	Standard treatment	Phase 2, Not yet recruiting	15/04/2020	University of Stanford
NCT04349241 Egypt	Favipiravir	Standard treatment	Phase 3, Not yet recruiting	16/04/2020	Universidade Ain Shams
NCT04351295 Egypt	Favipiravir	Placebo	Phase 2 and 3, Not yet recruiting	17/04/2020	University of Tanta
NCT04344600 United States	Interferon lambda alfa-1a	Placebo	Phase 2, Not yet recruiting	14/04/2020	Universidade Johns Hopkins
NCT04323761 United States	Remdesivir	No information		27/03/2020	Gilead Sciences
NCT04336904 Italy	Favipiravir	Placebo	Phase 3, Recruiting	08/04/2020	Asst Fatebenefratelli Sacco
NCT04347915 South Korea	Clevudine	Hydroxychloroquine	Phase 2, Not yet recruiting	17/04/2020	Bukwang Pharmaceutical
NCT04343976 United States	Interferon lambda	Standard treatment	Phase 2, Not yet recruiting	14/04/2020	Raymond Chung
NCT04324489 China	DAS181	No comparator	No information, Recruiting	27/03/2020	Renmin Hospital of Wuhan University
NCT04330690 Canada	Lopinavir/ ritonavir	Standard treatment	Phase 2, Recruiting	01/04/2020	Sunnybrook Health Sciences Centre
NCT04321174 Canada	Lopinavir / ritonavir	No intervention	Phase 3, Recruiting	25/03/2020	Darrell Tan
Antithyroid drugs					
NCT04348513 Greece	Triiodothyronine injection	Placebo	Phase 2, Not yet recruiting	16/04/2020	Uni-Pharma Kleon Tsetis AS Pharmaceutical laboratories
Antidepressants					
NCT04342663 Washington	Fluvoxamine	Placebo	Phase 2, em recruitment	13/04/2020	Faculty of Medicine of the University of Washington
Diuretics					
NCT04345887 Peru	Spironolactone	Placebo	Phase 4, Not yet recruiting	15/04/2020	University of Istanbul-Cerrahpasa

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
Analgesics					
NCT04350086 France	Dexmedetomidine	No information	Phase 4, Not yet recruiting	16/04/2020	University Hospital, Limoges
NCT04346615 United States	Vazegepant (BHV-3500)	Placebo	Phase 2 and 3, Recruiting	15/04/2020	Biohaven Pharmaceuticals, Inc
Antifibrinolytics					
NCT04338126 United States	Tranexamic acid	Placebo	Phase 2, Not yet recruiting	08/04/2020	University of Alabama em Birmingham
Antihypertensives					
NCT04335786 The Netherlands	Valsartan (Diovan)	Placebo	Phase 4, Recruitment	06/04/2020	University of Radboud
NCT04332666 Brazil	Angiotensin	Placebo	Phase 2 and 3, Not yet recruiting	03/04/2020	University Hospital Erasme
NCT04335123 United States	Losartan	No comparator	Phase 1, Recruiting	06/04/2020	University of Kansas Medical Center
NCT04340557 United States	Losartan	Standard treatment	Phase 4, Recruiting	09/04/2020	Sharp HealthCare
Antiarrhythmics					
NCT04351763 Poland	Amiodarone	Verapamil	Phase 2 and 3, Recruiting	17/04/2020	Nicolaus Copernicus University
Anti-fibrosis drugs					
NCT04334265 China	Anluohuaxian	No comparator	Recruitment	06/04/2020	Peking University First Hospital
NCT04337359 Switzerland	Ruxolitinib	No information	Accessible	07/04/2020	Novartis Pharmaceuticals
NCT04334044 Mexico	Ruxolitinib	No information	Phase 1 and 2, em recruitment	03/04/2020	Cooperative Group of Malignant Hemopathies
NCT04348071 United States	Ruxolitinib	No comparator	Phase 2 and 3, Not yet recruiting	15/04/2020	University of Colorado, Denver
NCT04338802 China	Nintedanib 150 MG	Placebo	Phase 3, Not yet recruiting	08/04/2020	Huilan Zhang
Antibiotics					
NCT04332107 United States	Azithromicyn	Placebo	Phase 3, Not yet recruiting	02/04/2020	University of California, San Francisco
Corticosteroids					
NCT04344288 France	Prednisone	Control group	Phase 2, Recruitment	14/04/2020	Civilian Hospitals of Lyon
NCT04348305 Denmark	Hydrocortisone	Placebo	Phase 3, Recruitment	16/04/2020	Scandinavian Critical Care Trials Group
NCT04344730 France	Dexamethasone	Placebo	Recruitment	14/04/2020	Assistance Publique - Hôpitaux de Paris
NCT04327401 Brazil	Dexamethasone	Standard treatment	Phase 3, Recruitment	31/03/2020	Luiz FL Reis, Ph.D.
NCT04330586 South Korea	Ciclesonide	Ciclesonide + hydroxychloroquine	Phase 2, Not yet recruiting	01/04/2020	Korea University Guro Hospital
Antidiabetics					
NCT04350593 United States	Dapagliflozin	Placebo	Phase 3, Recruiting	17/04/2020	Saint Luke's Health System

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
Immunomodulators					
NCT04349098 United States	Selinexor	Placebo	Phase 2, Recruiting	16/04/2020	Karyopharm Therapeutics Inc
NCT04340232 United States	Baricitinib	No comparator	Phase 2 and 3, Not yet recruiting	09/03/2020	University of Colorado, Denver
NCT04317040 United States	CD24Fc	Placebo	Phase 3, Recruiting	20/03/2020	OncoImmune, Inc.
NCT04331899 United States	Peginterferon Lambda-1a	Placebo	Phase 2, Recruiting	02/04/2020	Stanford University
NCT04326920 Belgium	Sargramostim	Standard treatment	Phase 4, Recruiting	30/03/2020	University Hospital, Ghent
NCT04335136 Multicenter	Human recombinant angiotensin 2 conversion enzyme (rhACE2)	Placebo	Phase 2, Not yet recruiting	06/04/2020	Apeiron Biologics
NCT04352465 Brazil	Dose escalation nanoparticles with methotrexate	No information	Phase 1 and 2 , Not yet recruiting	20/04/2020	Azidus Brazil
NCT04312997 United States	Inhalation solution PUL-042	Placebo	Phase 2, Not yet recruiting	18/03/2020	Pulmotect, Inc.
Immunosupressors					
NCT04341675 United States	Sirolimus	Placebo	Phase 2, Recruiting	10/04/2020	University of Cincinnati
Immunotherapy					
NCT04347681 Saudi Arabia	Convalescent plasma	No intervention	Phase 2, Recruiting	15/04/2020	King Fahad Specialized Hospital, Dammam
NCT04343144 France	Injection of Nivolumab	Standard treatment	Phase 2, Not yet recruiting	13/04/2020	Assistance Publique - Hôpitaux de Paris
NCT04347226 United States	BMS-986253	Standard treatment	Phase 2, Recruitment	15/04/2020	Matthew Dallos
NCT04345679 Hungary	Convalescent plasma	No information	Not yet recruiting	14/04/2020	Orthosera Kft.
NCT04342182 The Netherlands	Convalescent plasma	Standard treatment	Phase 2 and 3, Recruitment	10/04/2020	Medical Center Erasmus
NCT04345991 France	Convalescent plasma	Standard treatment	Phase 2, Not yet recruiting	15/04/2020	Assistance Publique - Hôpitaux de Paris
NCT04343755 United States	Convalescent plasma	No comparator	Phase 2, Recruiting	13/04/2020	Hackensack Meridian Health
NCT04321421 Italy	Hyperimmune plasma	No comparator	No information, Recruiting	25/03/2020	Foundation IRCCS San Matteo Hospital
NCT04338360 United States	Convalescent plasma	No information	Accessible	08/04/2020	Mayo Clinic
NCT04348656 Multicenter	Convalescent plasma	Standard treatment	Phase 3, Not yet recruiting	16/04/2020	Hamilton Health Sciences Corporation
NCT04353206 United States	Convalescent plasma	No information	Not yet recruiting	20/04/2020	Noah Merin
NCT04352751 Paquistan	Convalescent plasma	No information	Not yet recruiting	20/04/2020	Hilton Pharma
NCT04333355 Mexico	Convalescent plasma	No comparator	Phase 1, Not yet recruiting	03/04/2020	Hospital San Jose Tec de Monterrey

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04345523 Spain	Convalescent plasma	Standard treatment	Phase 2, Recruiting	14/04/2020	Prince of Asturias University Hospital
NCT04346446 India	Convalescent plasma	Random donor plasma + Support care	Phase 2, Recruiting	15/04/2020	Institute of Biliary and Liver Sciences, India
NCT04344535 United States	Convalescent plasma	Donor standard plasma	Phase 1 and 2, Registration through invitation	14/04/2020	Stony Brook University
NCT04346589 Italy	Convalescent plasma	No information	Not yet recruiting	15/04/2020	AO Ospedale Papa Giovanni XXIII
NCT04333251 United States	Convalescent plasma	Best support care	Not yet recruiting	03/04/2020	Baylor Research Institute
Cell therapies					
NCT04313322 Arabia	Mesenchymal stem cells	No information	Phase 1, em recruitment	18/03/2020	Stem cells Arabia
NCT04315987 Brazil	Mesenchymal stem cells	No information	Not yet recruiting	20/03/2020	Azidus Brazil
NCT04339660 China	Mesenchymal stem cells	Placebo	Phase 1 and 2, Recruiting	09/04/2020	Puren Hospital Affiliated to Wuhan University of Science and Technology
NCT04324996 China	Cells NK, cells IL15-NK, cells NKG2D CAR-NK, cells ACE2 CAR-NK, cells NKG2D-ACE2 CAR-NK	No information	Phase 1 and 2, Recruiting	27/03/2020	Chongqing Public Health Medical Center
NCT04346368 China	Mesenchymal stem cells	Placebo	Phase 1 and 2, Not yet recruiting	15/04/2020	Institute of Respiratory Diseases of Guangzhou
NCT04349631 United States	Mesenchymal stem cells	No information	Registration through invitation	16/04/2020	Hope Biosciences
NCT04338347 United States	Allogeneic cells derived from cardiosphere CAP-1002	No comparator	Available	08/04/2020	Capricor Inc.
NCT04336254 China	Mesenchymal, allogenic human stem cells of the dental pulp	Placebo	Phase 1 and 2, Recruiting	04/04/2020	Renmin Hospital of Wuhan University
NCT04348461 Spain	Mesenchymal stem cells	No comparator	Phase 2, Not yet recruiting	16/04/2020	Health Research Institute, Jiménez Díaz Foundation
Dietary supplements					
NCT04342689 United States	Dietary supplement containing resistant starch	Starch placebo	Phase 3, Not yet recruiting	13/04/2020	Yale University
NCT04334005 Spain	Vitamin D	Standard treatment	Not yet recruiting	03/04/2020	Universidad de Granada

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04347382 Paquistan	Mel / Nigella Sativa / Black Cumin	Standard treatment	Phase 3, em recruitment	15/04/2020	Sohaib Ashraf
NCT04344041 France	Vitamin D of 400.000 UI	Vitamin D3 standard dose	Phase 3, em recruitment	14/04/2020	University Hospital, Angers
NCT04351490 France	Zinc and Vitamin D3	Standard treatment	Not yet recruiting	17/04/2020	University Hospital, Lille
Chinese Traditional Medicine					
NCT04323332 China	Prescription of Chinese Traditional Medicine	Conventional treatment	Phase 3, Not yet recruiting	26/03/2020	Xiyuan Hospital of China Academy of Chinese Medical Sciences
Parasympathomimetics					
NCT04343963 Mexico	Deferoxamine	Standard treatment	Phase 1 and 2, Recruiting	06/04/2020	University of Medical Sciences of Kermanshah
Chelating agents					
NCT04333550 Iran	Deferoxamine	Standard treatment	Phase 1 and 2, Recruiting	06/04/2020	University of Medical Sciences of Kermanshah
Combined Therapies					
NCT04341038 Spain	Methylprednisolone and Tacrolimus	Usual care without intervention	Phase 3, Recruitment	01/04/2020	Hospital Universitari de Bellvitge
NCT04348474 Brazil	Hydroxychloroquine and Azithromicyn	No intervention	Suspended	16/04/2020	Azidus Brazil
NCT04343001 United Kingdom	Aspirin, losartan and simvastatin	Standard care	Phase 3, Not yet recruiting	13/04/2020	London School of Hygiene and Tropical Medicine, UK
NCT04341870 France	Sarilumab + Azithromicyn + Hydroxychloroquine	Sarilumab	Phase 2 and 3, Recruitment	10/04/2020	Assistance Publique - Hôpitaux de Paris
NCT04343092 Iraq	Ivermectin + Hydroxychloroquine + Azithromicyn	Placebo	Phase 1, Recruitment	13/04/2020	University of Bagdad
NCT04349410 United States	Hydroxychloroquine, Azithromicyn, Hydroxychloroquine, Doxycycline, Hydroxychloroquine, Clindamycin, Hydroxychloroquine, Clindamycin, Primaquine, Hydroxychloroquine, Clindamycin, Primaquine, Remdesivir, Tocilizumab, Methylprednisolone, Interferon-Alpha2B, Losartan, Convalescent serum	-	Phase 2 and 3, Registration through invitation	16/04/2020	Camelot Foundation

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04351919 Tunisia	Hydroxychloroquine and Azithromicyn	No information	Phase 4, Not yet recruiting	17/04/2020	Hospital Abderrahmane Mami
NCT04351191 Israel	Chloroquine and hydroxychloroquine	Dose regular e Placebo	Phase 4, Not yet recruiting	17/04/2020	Government of Punjab, Health and Specialized Medical Education Department
NCT04338698 Paquistan	Hydroxyquinoline + Oseltamivir + Azithromicyn	No intervention	Phase 3, Not yet recruiting	08/04/2020	Shehnoor Azhar
NCT04339712 Greece	Anakinra and Tocilizumab	No information	Phase 2, Recruitment	09/04/2020	Hellenic Institute for the Study of Sepsis
NCT04335552 United States	Hydroxychloroquine and Azithromicyn	Service standard	Phase 2, Recruitment	06/04/2020	Duke University
NCT04328012 United States	Lopinavir / ritonavir / Hydroxychloroquine sulfate / Losartan	Placebo	Phase 2 and 3, Recruitment	31/03/2020	Bassett Healthcare
NCT04324021 Italy	Emapalumab / Anakinra	Service standard	Phase 2 and 3, Recruitment	27/03/2020	Swedish Orphan Biovitrum
NCT04332835 Colombia	Convalescent plasma / Hydroxychloroquine /Azithromicyn	Service standard	Phase 2 and 3, Not yet recruiting	03/04/2020	Universidad del Rosario
NCT04315948 France	Remdesivir / Lopinavir / ritonavir / Interferon Beta-1A / Hydroxychloroquine	Service standard	Phase 3, Recruitment	20/03/2020	National Institute of Health and Medical Research, France
NCT04321616 Norway	Remdesivir / Hydroxychloroquine	Service standard	Phase 2 and 3, Recruitment	25/03/2020	University Hospital of Oslo
NCT04324463 Canada	Hydroxychloroquine / Chloroquine/ Azithromicyn / Interferon-Beta	Service standard	Phase 3, Recruitment	27/03/2020	Population Health Research Institute
NCT04347512 France	Azithromicyn-Hydroxychloroquine	Service standard	Phase 3, Not yet recruiting	15/04/2020	University Hospital, Strasburg, France
NCT04320277 Italy	Baricitinib / lopinavir / ritonavir	Service standard	Phase 2 and 3, Not yet recruiting	24/03/2020	Hospital of Prato
NCT04348695 Spain	Ruxolitinib / simvastatin	Service standard	Phase 2, Recruitment	16/04/2020	HM Investigation Foundation
NCT04331470 Iran	Levamisole Pill + Budesonide + Formoterol inhalator Lopinavir / Ritonavir + hydroxychloroquine	Service standard + Lopinavir / Ritonavir + hydroxychloroquine	Phase 2 and 3, Recruitment	02/04/2020	University of Medical Sciences of Fasa
NCT04344457 United States	Hydroxychloroquine / Indomethacin / Zithromax Oral Product	No information	Phase 1 and 2, Recruitment	14/04/2020	Perseverança Research Center, LLC
NCT04346147 Spain	Hydroxychloroquine/ Lopinavir / ritonavir/ Imatinib tablets / Baricitinib Oral Tablet	No information	Phase 2, Not yet recruiting	15/04/2020	Hospital Universitario de Fuenlabrada

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04333407 United Kingdom	Aspirin; Clopidogrel; Rivaroxaban; Atorvastatin; Omeprazole	No information	No information, recruiting	03/04/2020	Imperial College London
NCT04336332 United States	Hydroxychloroquine sulfate + Azithromicyn	Service standard	Phase 1 and 2, Recruitment	07/04/2020	Rutgers, New Jersey State University
NCT04321993 Canada	Lopinavir/ ritonavir; Hydroxychloroquine; Baricitinib	Standard treatment	Phase 2, Registration through invitation	26/03/2020	Nova Scotia Health; Authority Dalhousie University
NCT04339816 Czech Republic	Azithromicyn / Hydroxychloroquine	Placebo	Phase 3, Not yet recruiting	09/04/2020	Frantisek Duska, MD, PhD
NCT04350671 Iran	Interferon-β 1a + Lopinavir / Ritonavir + Hydroxychloroquine	Lopinavir / Ritonavir + Hydroxychloroquine	Phase 4, Registration through invitation	17/04/2020	Shahid Beheshti University of Medical Sciences
NCT04350684 Iran	Umifenovir + interferon-β 1a + lopinavir / ritonavir + hydroxychloroquine	Interferon-β 1a + lopinavir / ritonavir + hydroxychloroquine	Phase 4, Registration through invitation	17/04/2020	Shahid Beheshti University of Medical Sciences
NCT04347980 France	Dexamethasone and Hydroxychloroquine	Hydroxychloroquine	Phase 3, Recruitment	15/04/2020	Centre Chirurgical Marie Lannelongue
NCT04345276 China	Danoprevir + Ritonavir	No information	Phase 4, Recruiting	14/04/2020	Huoshenshan Hospital
NCT04353180 Egypt	Isotretinoin capsules (13 retinoic acid cis) + standard treatment / Isotretinoin (13 retinoic acid cis aerosol) + standard treatment	Standard treatment	Phase 3, Recruitment	20/04/2020	University of Kafrelsheikh
NCT04339426 United States	Atovaquone and Azithromicyn	No information	Phase 2, Recruitment	09/04/2020	Honor Health Research Institute
NCT04330638 Belgium	Anakinra; Siltuximab; Anakinra + Siltuximab; Tocilizumab; Anakinra + Tocilizumab	Standard treatment	Phase 3, Recruiting	01/04/2020	University Hospital, Ghent
NCT04334512 United States	Hydroxychloroquine, Azithromicyn, Vitamin C, Vitamin D and Zinc	No comparator	Phase 2, Not yet recruiting	06/04/2020	ProgenaBiome
NCT04345861 France	hydroxychloroquine + Azithromicyn	Hydroxychloroquine + placebo	Phase 2 and 3, Recruiting	15/04/2020	University Hospital, Montpellier
NCT04349592	Hydroxychloroquine + Azithromicyn	Hydroxychloroquine + Placebo	Not yet recruiting	16/04/2020	Hamad Medical Corporation
NCT04332094 Spain	Tocilizumab + hydroxychloroquine + Azithromicyn	hydroxychloroquine + Azithromicyn	Phase 2, Recruiting	02/04/2020	Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau

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Chart 7. Clinical trials registered for the management of COVID-19 (n = 202). (continuation)

Registration number, Country	Intervention (groups)	Control	Status	Registration Date	Funding
NCT04320238 China	Recombinant human interferon alpha-1B and alpha thymosin alpha 1 1timosina	No information	Phase 3, Recruiting	24/03/2020	Faculty of Medicine of the University of Shanghai Jiao Tong
NCT04351347 Egypt	Ivermectin + chloroquine / Nitazoxanide + chloroquine	No information	Phase 2 and 3, Not yet recruiting	17/04/2020	University of Tanta
NCT04341493 Mexico	Nitazoxanide + hydroxychloroquine	Hydroxychloroquine	Phase 4, Recruiting	10/04/2020	Hugo Mendieta Zeron
NCT04338906 Germainy	Camostat + Hydroxychloroquine	Placebo	Phase 4, Not yet recruiting	08/04/2020	University of Heinrich-Heine, Düsseldorf
NCT04322123 Brazil	Hydroxychloroquine + Azithromicyn	No intervention	Phase 3, Recruiting	26/03/2020	Heart Hospital
NCT04345289 Denmark	Convalescent plasma anti-SARS-CoV-2/ Sarilumab/ Baricitinib/ Hydroxychloroquine	Injectable placebo / placebo oral	Phase 3, Not yet recruiting	14/04/2020	Thomas Benfield
NCT04321278 Brazil	Hydroxychloroquine + Azithromicyn	Hydroxychloroquine	Phase 3, Recruiting	25/03/2020	Albert Einstein Israelite Hospital
NCT04345406 Egypt	Captopril or enalapril + chloroquine	Standard treatment + chloroquine	Phase 3, Not yet recruiting	14/04/2020	University of Tanta
NCT04347798 Canada	Hydroxychloroquine / Chloroquine	No information	Registration through invitation	15/04/2020	University of Alberta
NCT04347031 Russia	Mefloquine + Azithromicyn + / - tocilizumab	Standard treatment	Phase 2, Registration through invitation	15/04/2020	Federal Medical Biophysical Center of Burnasyan
NCT04341727 United States	Hydroxychloroquine sulfate / Azithromicyn/ chloroquine sulfate	Chloroquine + Azithromicyn	Phase 3, Recruiting	10/04/2020	Faculty of Medicine of the University of Washington
NCT04351724 Austria	Chloroquine or Hydroxychloroquine / Lopinavir / Ritonavir / Rivaroxaban / Thromboprophylaxis /Candesartan / anti-hypertensive non-SARS blockers / Clazakizumab	Placebo	Phase 2 and 3, Recruiting	17/04/2020	Medical University of Vienna
Chemical compounds					
NCT04343742 Colombia	Chlorine dioxide 3000 ppm	No information	Recruitment	13/04/2020	Genesis Foundation
Antiparasitics					
NCT04348409 Brazil	Nitazoxanide	Placebo	Recruiting	16/04/2020	No information

therapies, the focus on effective interventions to prevent mortality and other important outcomes for the patient, such as social isolation, advancing testing capacity, and preventive measures, can be reduced in the general population.

A search in different databases and repositories of prepress papers and an evaluation of the methodological quality of the included studies were performed to identify studies on the theme. However, the evidence found has critical methodological weaknesses, such as a limited number of participants and a lack of control or conventional group[17,21].

In one of the studies, the two arms of the study received HCQ (high-dose and low-dose), which did not allow to evaluate the effect of HCQ in comparison with placebo or standard treatment[15]. Other limitations are the heterogeneity of the included studies concerning different dosages, routes, and duration of administration. Moreover, we were unable to detail the treatments described as standard in all studies.

There are some restrictions on the synthesis of evidence. In this synthesis, an assessment of the set of evidence generated was not conducted, employing The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[60] approach, due to the heterogeneity between the studies, which evaluated neither exposures nor similar outcomes. This rapid review evidenced few overlaps between individual studies underlying the systematic reviews. Only nine duplications were identified in the three reviews included, which contained 48 primary studies.

Final considerations

Despite the various drug options identified, scientific evidence is still incipient and of low methodological quality. There is no proven efficacy and safety of any medication for human coronavirus infections. Thus, it is necessary to carry out randomized controlled clinical trials with adequate follow-up time and methods disclosed and subject to scientific peer review. Furthermore, dozens of clinical studies evaluating the efficacy and safety of drugs are underway worldwide. Periodic updating of this review is recommended to monitor scientific evidence as it becomes available.

Collaborations

KRC Andrade, VKS Carvalho, CM Farinasso, AA Lima, RB Silva and VK Wachira participated in the planning, search, extraction, selection and evaluation of the quality of the studies, data analysis, writing and revision of the manuscript. HC Capucho, PM Souza, T Vanni, DF Rêgo and CG Sachetti participated in the critical review of the manuscript.

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