Effectiveness and safety of antiviral or antibody treatments for coronavirus

Patricia Rios, Amruta Radhakrishnan, Jesmin Antony, Sonia M. Thomas, Mathew Muller, Sharon E. Straus, Andrea C. Tricco

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Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences University of Oxford
Li Ka Shing Research Institute, Knowledge Translation Program, St. Michael's Hospital

Correspondence to Andrea.Tricco@unityhealth.to

VERDICT

The current evidence for the effectiveness and safety of antiviral therapies for coronavirus is inconclusive and suffers from a lack of well-designed prospective trials or observational studies, preventing any treatment recommendations from being made. However, it is clear that the existing body of evidence is weighted heavily towards ribavirin, which has not shown conclusive evidence of effectiveness and may cause harmful adverse events so future investigations may consider focusing on other candidates for antiviral therapy.

BACKGROUND

The Infectious Disease Prevention and Control Branch of the Public Health Agency of Canada (PHAC) commissioned this rapid review on the effectiveness and safety of antiviral, antibody, or other medical countermeasures for the treatment of novel coronavirus (COVID-19). The overall objective of this rapid review was to identify safe and effective medical countermeasures to address the current outbreak of a novel coronavirus (COVID-19). In order to focus the research question to increase feasibility, we proposed the following key research questions:

1. What is the effectiveness and safety of any antiviral and/or monoclonal antibody treatment currently available to treat (COVID-19)?
2. What is the effectiveness and safety of currently available antiviral therapies used to treat other coronavirus infections?

CURRENT EVIDENCE

54 studies were included in the review: three controlled trials[1-3], 10 cohort studies[4-13], seven retrospective medical record/database studies[14-20], and 34 case reports or series[21-54]. These studies included patients with severe acute respiratory syndrome (SARs, n=33), middle east respiratory syndrome (MERS, n=16), COVID-19 (n=3)[30,51,52], and unspecified coronavirus (n=2). The most common treatment was ribavirin (n=41), followed by oseltamivir (n=10) and the combination of lopinavir/ritonavir (n=7). Additional therapies included broad spectrum antibiotics (n=30), steroids (n=39) or various interferons (n=12). No eligible studies examining monoclonal antibodies for COVID-19 were identified.

One trial[3] found that ribavirin prophylactic treatment statistically significantly reduced risk of MERS infection in people who had been exposed to the virus. Of the 21 studies[1,9,10,12,14,15,20,28,29,32,35,37,39,40,42,45,46,48,50-52] reporting rates of ICU admission in hospitalized SARS or MERS patients, none reported statistically significant results in favour of or against antiviral therapies. Of the 40 studies[1,3-22,24,28,29,35,37,39-42,44-51,53] reporting mortality rates in hospitalized SARS or MERS patients, one cohort study[5] (MERS) and one retrospective study (SARS)[15] found a statistically significant increase in the mortality rate for patients treated with ribavirin. Eighteen studies[2,4-6,8-10,12,15,16,20,23,33,34,37,38,45,46] reported potential drug-related adverse effects including gastrointestinal symptoms, anemia, and altered liver function in patients receiving ribavirin

Summary Study and Patient Characteristics

Characteristics (n)	Controlled Trials (n=3)	Cohort Studies (n=10)	Retrospective Studies (n=7)	Case Reports/Series (n=34)
Diagnosis				
COVID-19	--	--	--	3
SARS	2	7	4	20
MERS	1	3	3	9
Other coronavirus	--	--	--	2
Age of population (range)	22 to 57	15 to 70	22 to 79	4 months to 83 years
Sample size [median (range)]	43 (16 to 190)	169 (72 to 1934)	63 (14 to 306)	8 (1 to 323)
Publication Year (range)	2004 to 2019	2003 to 2019	2003 to 2019	2003 to 2020
Country of conduct	China (2), South Korea (1)	China (3), Hong Kong (3), South Korea (1), Saudi Arabia (2), Singapore (1)	Canada (2), Saudi Arabia (3), Taiwan (2)	Canada (3), China (7), France (1), Germany (1), Greece (1), Hong Kong (11), South Korea (2), Saudi Arabia (5),

				Taiwan (1), United Arab Emirates (1), USA (1)
Comorbidities reported in study population	No (3)	Yes (6); No (4)	Yes (5), No (2)	Yes (22), No (12)
Interventions		9		
Ribavirin	3	2	7	29
Oseltamivir	--	2	1	7
Lopinavir/ritonavir	1	2	1	3
Foscarnet	--	--	--	1
Remdesivir	--	--	--	1
Antibiotics	2	3	3	22
Steroids	2	10	5	22
Interferons	1	3	2	6

EMERGING EVIDENCE IN COVID-19

Three studies examining patients infected with COVID-19 were included in this review: one case report[30] and two case series[51,52].

The case report[30] included a 35-year-year old man, the first American diagnosed with COVID-19. He was initially treated with vancomycin and cefepime which are standard treatments for suspected community-acquired pneumonia. Upon lab-confirmation of COVID-19 infection, the antibiotics were stopped and the patient was started on Remdesivir 7 days after initial admission to hospital. At study end, the patient remained hospitalized with the majority of symptoms resolved.

The two case series[51,52] were conducted in China and included 4 and 138 patients, respectively. All patients were hospitalized and initial diagnosis was made based on WHO Criteria later confirmed by lab-testing of the patient specimens. The case series included an approximately even number of male and female (55% v 45%) patients ranging in age from 19 to 68 years old, with a variety of co-morbidities including cardiovascular disease, chronic kidney or liver disease, COPD, and diabetes.

In one case series[52], patients (n=4) were treated with a combination of lopinavir/ritonavir, Arbidol (umifenovir), antibiotics, Shufeng Jiedu Capsule (Traditional Chinese Medicine), and intravenous immunoglobulins. At study end (15 days), two patients tested negative for COVID-19 and were subsequently discharged from the hospital and two patients remained hospitalized, one of whom still required mechanical ventilation. In the larger case series[51], 124 patients were treated with oseltamivir combined with antibiotic therapy in 89 patients and combined with glucocorticoids in 62 patients. Over the course of the study, 34 patients treated with oseltamivir were admitted to the ICU, 17 of which required invasive mechanical ventilation. At study end (19

days), 47 patients had been discharged and 6 patients died, all of whom had been admitted to ICU.

Ongoing human trials for COVID-19

Four currently ongoing randomized controlled trials proposing to test treatments for COVID-19 were identified through keyword searches of clinicaltrials.gov (as of February 11, 2020). All four trials are being carried out in China, three are investigating antiviral medications (lopinavir/ritonavir, arbidol (umifenovir), darunavir, cobicstat, and, ASC09/ritonavir) and one trial is investigating a combination of lopinavir/ritonavir with Traditional Chinese Medicines (TCM). At the time of this writing two of the trials have started recruiting patients.

Details of ongoing COVID-19 trials (as of Feb 11, 2020)

Author, Year Country NCT ID	Status Estimated Enrollment Estimated completion	Eligibility Criteria (age; diagnosis) Interventions
Li, 2020 **China** **NCT04252885**	Recruiting 125 participants July 31, 2020	Adult (18-80 yrs); lab-confirmed infection Group A: standard treatment + lopinavir/ritonavir Group B; standard treatment + arbidol (umifenovir) Group C: standard treatment
Lu, 2020 **China** **NCT04252274**	Not yet recruiting 30 participants December 31, 2020	All ages; National Health Commission diagnostic criteria Intervention: Darunavir, Cobicistat + conventional treatments Comparator: Conventional treatments
Qiu, 2020 **China** **NCT04261907**	Not yet recruiting 160 participants June 30, 2020	Adult (18-75 yrs); lab-confirmed infection Intervention: ASC09/ritonavir + conventional treatment Comparator: lopinavir/ritonavir + conventional treatment
Xiao, 2020 **China** **NCT04251871**	Recruiting 150 participants January 22, 2021	Youth/Adult (14-80 yrs); lab-confirmed infection Intervention: TCM + conventional medicines** Comparator: Conventional medicines**

**Conventional medicines includes: oxygen therapy, antiviral therapy (alfa interferon via aerosol inhalation, and lopinavir/ritonavir, 400mg/100mg, p.o, bid)

CONCLUSIONS

- The results of the included studies proved inconclusive on the effectiveness of antiviral drugs in treating coronavirus infections and prevent any particular treatments from being recommended for use
- Important safety signals were identified in the included studies, particularly the possible development of anemia and altered liver function in patients receiving ribavirin treatment
- The existing body of evidence is weighted heavily towards studies of ribavirin which has shown no particular efficacy in treating coronavirus and may in fact cause harmful adverse effects
- Future investigations into potential antiviral therapies for coronavirus may be best served by pointing their attention to other drug candidates

medrxiv.rog pre-print link: https://www.medrxiv.org/content/10.1101/2020.03.19.20039008v1

End.

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SEARCH TERMS

Comprehensive literature searches addressing both research question 1 (RQ1) and research question 2 (RQ2) were developed by an experienced librarian for MEDLINE, EMBASE, the Cochrane Library, and biorxiv.org/medrxiv.org databases. Search terms included MeSH subject headings (e.g., Antiviral Agents, Interferon, Antibodies – Monoclonal, etc.) and key word terms (e.g., coronavirus, SARS, medical countermeasures, etc.). Grey (i.e., difficult to locate or unpublished) literature was located using keyword searches of relevant terms (e.g. coronavirus, SARS, etc.) in clinicaltrials.gov and GIDEON (Global Infectious Diseases and Epidemiology Network). Additionally, the final set of included articles was cross-referenced with a list studies provided by our knowledge users from the Public Health Agency of Health as part of the scoping process for this review.

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