TREATMENT FOR COVID-19 IS URGENTLY NEEDED AND SEVERAL POTENTIAL MEDICINES ARE BEING EVALUATED IN THE WHO-LED SOLIDARITY CLINICAL TRIAL FOR WHICH RECRUITMENT IS ALSO PLANNED FOR SOUTH AFRICA.

WE CONDUCTED A RAPID REVIEW OF AVAILABLE CLINICAL EVIDENCE ABOUT USE OF INTERFERONS WITH OR WITHOUT OTHER MEDICINES FOR HOSPITALISED PATIENTS WITH COVID-19.

WE FOUND NO SYSTEMATIC REVIEWS, OR CONTROLLED STUDIES ON THIS TOPIC. WE IDENTIFIED FOUR CASE SERIES (SINGLE ARM COHORTS) FROM CHINA IN WHICH ALL PATIENTS RECEIVED INHALED INTERFERON.

AS THE STUDIES DID NOT HAVE ANY COMPARATOR GROUP AND ALL PATIENTS RECEIVED INTERFERONS, WE ARE UNABLE TO DETERMINE WHETHER INTERFERONS INFLUENCE OUTCOMES.

NO REPORTS ON THE USE OF INTERFERONS IN CHILDREN WITH COVID-19 WERE IDENTIFIED AND THEIR USE IS DISCOURAGED OUTSIDE OF A CLINICAL TRIAL SETTING.

THERE IS CURRENTLY INSUFFICIENT EVIDENCE TO SUPPORT INCLUSION OF INTERFERON IN TREATMENT GUIDELINES FOR COVID-19 IN SOUTH AFRICA UNTIL FURTHER EVALUATIONS ARE CONDUCTED OR REPORTED.

ELIGIBLE PATIENTS WITH COVID-19 IN SOUTH AFRICA SHOULD BE CONSIDERED FOR ENROLMENT IN RELEVANT THERAPEUTIC TRIALS.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

- Interferon not be included on the National Department of Health COVID-19 Guidelines and that patients eligible for interferon be enrolled in the relevant clinical trial.
- The proposed recommendation was accepted by the Clinicians Ministerial Advisory Committee on Covid-19 at the meeting of 31 March 2020.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.
BACKGROUND

The novel human respiratory coronavirus (SARS-CoV-2), which is the cause of COVID-19, was declared a pandemic on 11 March 2020. There are currently more than 600,000 confirmed COVID-19 cases in over 200 countries and SARS-CoV-2 has caused more than 31,000 deaths (WHO 2020; as at 1pm 29 March, 678,720 confirmed cases, 31,700 deaths; https://coronavirus.jhu.edu/map.html).

Effective therapeutic options to manage hospitalised patients with COVID-19 cases need to be urgently identified. Interferon have been suggested as possible treatment for COVID-19 patients. Type 1 interferons are part of human cellular defences against viral infections. Type 1 interferons mediate suppression of viral replication; they suppress messenger RNA translation and protein synthesis. Interferons also induce changes within cells to make it more likely that the adaptive immune response can recognise infected cells. These mechanisms are also required for normal functioning of cells, which means that interferons have the potential to cause harm by interfering with normal cellular function.

Interferons have previously been investigated as treatment for other coronavirus infections. Use of recombinant interferons in combination with ribavirin was explored in MERS-CoV, with little evidence for efficacy (Kain 2020; https://www.cdc.gov/coronavirus/mers/index.html). There was also no clear evidence for efficacy in treatment of SARS-CoV (Stockman 2006).

Although there may be biological plausibility for the role of interferons in treating COVID-19, their efficacy, safety, dosing and ideal timing of delivery has yet to be determined through prospective comparator clinical trials. In the interim, it is necessary to understand the available evidence for their use.

RESEARCH QUESTION: Should interferons be used for managing COVID-19?

METHODS

We conducted a rapid review of the evidence including systematic searching of two electronic databases (PubMed and the Epistemonikos). Screening of records and data extraction was conducted by one reviewer, with results reviewed and checked by another reviewer. Relevant records were extracted in a narrative table of results. No appraisal or meta-analysis was done. The search strategy is shown in Appendix 1.

Eligibility criteria for review

Population: Patients hospitalised with confirmed COVID-19, no age restriction.

Intervention: Type 1 interferon/s either alone or in combination with another medicine. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator)

Outcomes: Mortality, duration of hospitalisation, duration of viraemia, duration of ICU stay, duration of respiratory support, adverse reactions.

Study designs: Case reports, case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies in humans.
RESULTS

We searched PubMed and the Epistemonikos electronic databases on 29 March 2020. Details of each search are provided in Appendix 1. All records were uploaded into EndNote. One reviewer screened 62 records and identified four potentially eligible articles. Data in Table 1 report the main characteristics and outcomes of the included studies. Table 2 describes planned trials found during the search.

Of the included studies, there were two prospective cohorts (case series) and two retrospective case series, all from China. Chinese guidelines recommend inhaled alpha-interferon for all hospitalised patients (5 million U or equivalent for adults, adding 2ml of sterilized water, atomized inhalation twice daily) (weak level of evidence) (Jin 2020). None of the included observational studies had a comparator arm where patients did not receive interferon.

In the included studies, interferons were often used with other medicines, including other antivirals (ribavirin, lopinavir + ritonavir, abidor), corticosteroids and antibacterials (specific antibiotics were not described).

Quality appraisal of included studies was not done. However, all of these studies are observational and none of them included a comparator arm which did not receive interferon. They therefore cannot inform the assessment of efficacy or safety of interferons in the treatment of COVID-19.

CONCLUSION

There is currently insufficient evidence to support inclusion of interferon in treatment guidelines for COVID-19 in South Africa until further evaluations are conducted or reported. Eligible patients in South Africa should be considered for enrolment in randomised clinical trials of potential therapies for COVID-19 (e.g. the SOLIDARITY trial), so that robust data on efficacy and safety of interventions can be generated to inform treatment policies going forward.

Reviewers: Tamara Kredo, Karen Cohen.

Declaration of interests: TK (Cochrane South Africa, South African Medical Research Council), KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) have no interests to declare in respect of interferon therapy for COVID-19.

REFERENCES


<table>
<thead>
<tr>
<th>Citation</th>
<th>Study design</th>
<th>Population (n)</th>
<th>Treatment</th>
<th>Main findings</th>
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<tr>
<td>Abstract only</td>
<td>Prospective cohort to compare triple vs dual treatment and timing of triple therapy [dates not clear]</td>
<td>Setting: China, 15 medical institutions of Zhejiang Province Patients: hospitalized with COVID-19 pneumonia Sample size: possibly 236</td>
<td>All patients were treated with recombinant interferon α-2b (5 million U, 2 times/d) aerosol inhalation. 196 patients were treated with abidol (200 mg, 3 times/d) + lopinavir + ritonavir (dose unclear) as the triple combination antiviral treatment group. 41 patients were treated with lopinavir + ritonavir (dose unclear) as the dual combination antiviral treatment group. Sub-group analysis: patients who received triple combination antiviral therapy divided into three groups: within 48 hours, 3-5 days and &gt; 5 days after the symptom onset.</td>
<td>Cannot determine efficacy or safety of interferon as all patients received this therapy. The time to virus nucleic acid negative was 12.2 ± 4.7 days in the triple combination antiviral drug group, which was shorter than that in the dual combination antiviral drug group (15.0 ± 5.0) days (t = 6.159, P &lt; 0.01). The length of hospital stay [12 days (9, 17)] in the triple combination antiviral drug group was also shorter than that in the dual combination antiviral drug group [15 days (10, 18)] (H = 2.073, P &lt; 0.05). Comparing the antiviral treatment which was started within 48 hours, 3-5 days and &gt; 5 days after the symptom onset to the negative test of viral shedding was 13 (10,16.8), 17 (13,22) and 21 (18-24) days respectively (Z = 32.983, P &lt; 0.01), and the time from antiviral therapy to the negative test of viral shedding was (11.8±3.9), (13.5±5.1) and (11.2±4.3) d. The differences among the three groups were statistically significant (Z=32.983 and 6.722, P &lt;0.01 or&lt;0.05)</td>
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<td><strong>Published, peer reviewed</strong>&lt;br&gt;Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical Features and Treatment of COVID-19 Patients in Northeast Chongqing. Journal of medical virology. 2020.&lt;br&gt;<a href="https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25783">https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25783</a></td>
<td>Prospective case series&lt;br&gt;Period: Jan 23 – Feb 8, 2020</td>
<td>Setting: China, Chongqing&lt;br&gt;Patients: 135 hospitalized of which 40 had severe disease and 95 mild disease (criteria for mild versus severe not specified). Age: 47 years (IQR 36-55), and there was no significant gender difference (53.3% men) Forty-three (31.9%) patients had underlying disease, primarily hypertension (13 [9.6%]), diabetes (12 [8.9%]), cardiovascular disease (7 [5.2%]), and malignancy (4 [3.0%]) Patients with severe disease were older and more likely to have comorbidities. All patients had radiographic evidence of lung involvement.</td>
<td>135 patients received: lopinavir + ritonavir and interferon. 59 received antibacterial therapy 36 received corticosteroids. 124 patients received traditional Chinese medicine too.</td>
<td>Cannot determine efficacy or safety of interferon as all patients received this therapy. By Feb 8, 5 patients had been discharged, one patient had died</td>
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<td><strong>Online only, not peer reviewed</strong>&lt;br&gt;Liu I, Gao J-y. Clinical characteristics of 51 patients discharged from hospital with COVID-19 in Chongqing, China. 2020.&lt;br&gt;<a href="https://www.medrxiv.org/content/medrxiv/early/2020/02/23/2020.02.20.20025536.full.pdf">https://www.medrxiv.org/content/medrxiv/early/2020/02/23/2020.02.20.20025536.full.pdf</a></td>
<td>Retrospective, single-center case series&lt;br&gt;Period: Jan – Feb 2020</td>
<td>Setting: China, Chongqing University, Three Gorges Hospital&lt;br&gt;51 Patients admitted between January 20 to February 3, 2020 Discharged January 29 to February 11, 2020 44 non-severe; 7 severe Median age was 45 years</td>
<td>All received aerosolised inhalation of recombinant human interferon a-1b for injection and oral antiviral therapy with lopinavir + ritonavir, duration not specified. Most patients were given Bacillus licheniformis capsules regulated intestinal flora treatment (44 [86.3%]). 10 patients (19.6%) received short-term (3-5 days) glucocorticoid treatment.</td>
<td>Cannot determine efficacy or safety of interferon as all patients received this therapy. 1 patient died All others discharged</td>
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<td>Google translated article, English abstract available</td>
<td>Retrospective case series&lt;br&gt;Period: January 20 to February 6, 2020</td>
<td>(interquartile range, 34-51; range, 16-68 years) and 32 (62.7%) were men.</td>
<td>134 patients received recombinant human interferon α2b spray treatment and symptomatic supportive treatment.&lt;br&gt;52 patients took the antiviral drug lopinavir + ritonavir, 34 patients took the antiviral drug abidol, and 48 patients did not take any antiviral medication.</td>
<td>Cannot determine efficacy or safety of interferon as all patients received this therapy.</td>
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<td><strong>SOLIDARITY trial</strong></td>
<td>Prospective randomised controlled clinical trial</td>
<td>COVID-19 patients hospitalised with severe illness</td>
<td>Local standard of care alone, OR local standard of care plus one of • Remdesivir (daily infusion for 10 days) • Chloroquine or hydroxychloroquine (oral loading dose, then orally twice daily for 10 days) • Lopinavir + Ritonavir (orally twice daily for 10 days) • Lopinavir + Ritonavir (as above) plus Interferon (daily injection for 10 days).</td>
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<td><strong>Tongji H. Efficacy and Safety of IFN-α2β in the Treatment of Novel Coronavirus Patients. clinicaltrialsgov. 2020.</strong></td>
<td>Open-label, single center, prospective, randomised controlled clinical trial Planned sample size 108 patients.</td>
<td>Country: China, Chongqing Public Health Medical Center. Eligibility: Mild to moderate COVID-19 in 18 – 65 yo patients Criteria: 2019-nCoV RNA detection is positive in the upper respiratory tract (URT) via nasopharyngeal or oropharyngeal swab samples, or lower respiratory tract (LRT) via expectorated sputum samples, endotracheal aspirate samples, or bronchoalveolar lavage samples of enrolled patients; (2) Patients are symptomatic, with fever, unproductive cough or dyspnea, and their X-ray or CT scan imaging demonstrates Three therapeutic regimens: ribavirin plus IFN-α1b (arm A); lopinavir + ritonavir plus IFN-α1b (arm B); and ribavirin plus lopinavir + ritonavir plus IFN-α1b (arm C) Dosing: Ribavirin (intravenous loading dose of 2 g, followed by oral doses of 400–600 mg every 8 h depending on the patients weight, for 14 days); lopinavir + ritonavir (oral, 400 mg/100 mg per dose, twice a day, for 14 days); and IFN-α-1b (atomizing inhalation, 5 million U or 50 μg per dose, twice a day, for 14 days).</td>
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<td>Could be same as above</td>
<td>interstitial pneumonia; (3) Respiratory rate (RR) &lt; 30 breaths/min; (4) Arterial oxygen saturation (resting-state) &gt; 93%; (5) Arterial partial pressure of oxygen (PaO2) /oxygen concentration (FiO2) &gt; 300 mmHg.</td>
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### Appendix 1: Search strategy

**Epistemonikos**

(ttitle:(coronavirus or covid* or 2019-ncov or sars-cov-2) or abstract:(coronavirus or covid* or 2019-ncov or sars-cov-2)) and (title:(interferon or interferon* or ifn or ifn*) or abstract:(interferon or interferon* or ifn or ifn*))

Output 29 records, 27 after removing duplicates

**PubMed**


And ("2019/12/01"[date - publication] : "3000"[date - publication])

Output 33 records, 31 after removing duplicates