South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: TYPE 1 INTERFERONS FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 9 April 2021 *(third update of initial report of 29 March 2020)*

Key findings

- We updated the rapid review of evidence for the use of type 1 interferons compared to standard of care for hospitalised patients with COVID-19. The search for this update was conducted on 1 March 2021.
- In this update, we identified an additional multicentre randomised controlled trial, the Solidarity trial (Pan et al).

  The Solidarity trial assessed 28-day all-cause death in 2050 participants who received interferon β versus 2050 receiving standard of care. Treatment with subcutaneous interferon β did not result in 28 day-mortality benefit. Mortality was 12.9% (243/2050) in the interferon arm versus 11.0% (216/2050) in the standard of care arm, rate ratio for death 1.16 (95% confidence interval 0.96 to 1.39); there may be 17 more deaths per 1000 people treated with interferon compared to no treatment (ranging from 4 fewer to 41 more deaths).

  We did not identify any reports on the use of interferons in children with COVID-19.
- The current evidence does not support inclusion of interferons in treatment guidelines for COVID-19 in South Africa.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	X				

Recommendation: We recommend against the use of type 1 interferon for the treatment of COVID-19 in hospitalised patients.
Rationale: No mortality benefit, and type 1 interferons are expensive.
Level of Evidence: IV RCTs of very low quality
Review indicator: New evidence of efficacy and safety

(Refer to appendix 3 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available as outlined in the current Terms of Reference for the committee work.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	29 March 2020	TK, KC	Insufficient evidence to support use of interferon. May be used in a clinical trial setting.
Second	31 July 2020	TK, KC, YB	Recommendation retained as above, noting that interferon is cost-prohibitive. Evidence and EtD updated, including an ITT with sensitivity analyses.
Third	24 November 2020	n/a	Statement advising that rapid review will be updated when the results from the WHO SOLIDARITY trial are available in peer review format.
Fourth	8 April 2021	TK, KC, NT	Review updated with SOLIDARITY results. Recommendation updated against the use of subcutaneous interferon type 1 for the treatment of COVID-19 in hospitalised patients.

BACKGROUND

Effective therapeutic options to manage hospitalised patients with COVID-19 cases need to be urgently identified. Type 1 interferons have been suggested as a 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).

There are several reports from observational studies about use of interferons, some of which were described in our first rapid review report (Wei 2020, Wan 2020, Jiu 2020, Jun 2020, Pereda 2020). Observational cohort studies are subject to bias and confounding. Methodological limitations, including prognostically important differences in baseline characteristics between groups make it difficult to reach robust conclusions about efficacy and safety. As randomised trials of type 1 interferons versus standard of care have now been completed, we have restricted this update of the rapid review to findings of randomised trials comparing type 1 interferon to placebo/standard of care.

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

METHODS

Based on an *a priori* planned rapid review method, we conducted an update to the previous rapid reviews (29 March and 31 July 2020) including systematic searching of three electronic databases: Epistemonikos, Cochrane COVID study register and COVID Living Reviews database (www.covid-nma.com) on 1 March 2021 (see Appendix 1). Screening of records and data extraction was conducted in duplicate (KC, TK). Relevant records were extracted in a narrative table of results.

For the outcomes of mortality, duration of hospitalization, adverse events and serious adverse events we reported from the trials directly.

For the outcome progression to mechanical ventilation (WHO score 6 and above) we extracted data from the Living review found on the www.covid-nma.com site. This review follows a pre-specified protocol including duplicate extraction, appraisal using the Cochrane Risk of Bias 2.0 tool and assessment of the overall quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to understand the impact of methodological issues, imprecision, heterogeneity, applicability or directness of the trial to the question, on the overall certainty of the evidence.

Eligibility criteria for review

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

Intervention: Type 1 interferon. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Standard of care/placebo.

Outcomes: Mortality; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse events, adverse reactions.

Study designs: Randomised controlled trials, and systematic reviews of randomised controlled trials.

RESULTS

Search results

Our updated search identified 172 new records after removing 72 duplicates. Two reviewers (TK, KC) screened these,

identifying three trials to be added - Pan 2020 (SOLIDARITY trial); Rahmani 2020; and Monk 2020 - to the included trial in our previous review (Davoudi-Monfared 2020). A search on 14 March 2020 on www.covid-nma.com found no additional trials. All four trials are included in the COVID Living Reviews database on the www.covid-nma.com website.

Table 1 reports the main characteristics and outcomes reported in the included clinical trials. **Table 2** reports the planned ongoing trials as found on the COVID Living Reviews website as of 18 March 2021.

Description of included trials

- **Interferon β vs Standard care/Placebo**

Three trials investigated this comparison: Pan *et al* (SOLIDARITY) is a multinational randomised controlled trial which included 11330 adults from 30 countries, of which 2063 were randomised to subcutaneous interferon β (651 in combination with lopinavir/ritonavir), and 2064 to standard of care without interferon β (low risk of bias). Davoudi-Monfared *et al*. was a randomised controlled trial conducted in hospitalised patients with severe COVID-19 in Iran, 92 participants randomised and 81 included in the analysis (high risk of bias due to selection bias and missing outcome data). Rahmani *et al* is an open label randomised trial in 80 patients in Iran (some concerns of bias due to lack of blinding and potential selective outcome reporting). See table 1 for detailed description.

Outcomes of interest

- ***Mortality:*** In the Solidarity trial, treatment with subcutaneous interferon β did not result in 28-day mortality benefit. The modified ITT analysis included 2050 participants who received interferon β and 2050 receiving standard of care (13 participants in the interferon β arm and 14 in the standard of care of arm were excluded from the intention to treat analysis because no/unknown consent to follow-up).

  Mortality was 12.9% (243/2050) in the interferon arm versus 11% (216/2050) in the standard of care arm, rate ratio for death 1.16 (95% confidence interval 0.96 to 1.39).

  We have not included the covid-nma.com random effects meta-analysis for 28-day mortality in this update, as that analysis included Davoudi-Manfared et al, and Rahmani et al, which were assessed as having substantial risk of bias, and few mortality events.

- ***Duration of hospitalization:*** Only reported in 1 trial (Davoudi-Monfared et al) Length of hospital stay (days ± SD) was similar IFN arm 14.80 ± 8.45 vs 12.25 in the standard of care arm ± 7.48, p= 0.69.
- ***Duration of viraemia:*** not reported.
- ***Duration of ICU stay:*** not reported
- ***Progression to mechanical ventilation (WHO ordinal scale 6 or above):*** 10/83 in the IFN group compared to 22/82 in the control group RR 0.46 (95% CI 0.24 to 0.90). Two trials included: Rahmani et al, Davoudi-Monfared et al)
- ***Adverse events:***
  - *Solidarity trial (Pan et al):* adverse events not reported
  - *Interferon vs standard of care (Rahmani):* Injection site reactions 2 (6%) vs 0, flu-like syndrome 4 (12%) vs 0, ARDS 6 (18%) vs 2 (6%), secondary infections/ septic shock 1 (3%) vs 4 (12%), AKI 3 (9%) vs 4 (12%), AHI 2 (6%) vs 5 (15%).
  - *Interferon vs standard of care (Davoudi Monfared):* Acute kidney injury 12 (29%) vs 11 (28%), p=0.58, nosocomial infections 11 (26%) vs 5 (13%) p=0.09, septic shock 10 (24%) vs 7 (18%), p=0.35, hepatic failure 5 (12%) vs 9 (23%), p=0.15, DVT 1 (2%) vs 0, p=0.51, hypersensitivity reactions 1 (2%) vs 0 p=0.51, IFN-related injection reactions 8(19%) vs 0, neuropsychiatric problems 4 (10%) vs 0 p=0.06, indirect hyperbilirubinemia 1 (2%) vs 1 (3%) p= 0.73)
- ***Serious adverse events/reactions:*** not specifically reported.

- **Inhaled nebulised interferon beta-1a vs Placebo**

Monk *et al* is a randomised controlled, double blind trial in 101 hospitalised patients in the United Kingdom.

Outcomes of interest

- ***Mortality:*** up to 28 days no deaths in intervention group, 3 in SOC group
- ***Duration of hospitalization:*** Not reported

- ***Duration of viraemia:*** not reported.
- ***Duration of ICU stay:*** not reported
- ***Progression to mechanical ventilation (WHO ordinal scale 6 or above):*** Placebo group, 5 (10%) participants underwent intubation/ died between the first dose and day 15 or 16 versus 3 (6%) in the intervention group.
- ***Adverse events:*** Treatment-related treatment-emergent adverse event: 7(15%) with intervention (cough (2), decreased oxygen saturation (1), diarrhoea (1), dry throat (1), oral pain (1), night sweats (1), tremor (1)) versus 2 (4%) SOC.
- ***Serious adverse events:*** Serious treatment emergent adverse events 7 (15%) vs 14 (28%). None assessed by investigators as being caused by intervention.

CONCLUSION

In this update of the rapid review, we included four RCTs including the multi-national SOLIDARITY trial. We found no studies in children. Based on the available data, we recommend against the inclusion of type 1 interferons in treatment guidelines for COVID-19 in South Africa.

Reviewers: Tamara Kredo, Karen Cohen, Ntombifuthi Blose

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

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Table 1. Characteristics of included trials

Citation	Study design	Population	Treatment	Main findings	Risk of Bias assessment
Monk et al, Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomized, double-blind, placebo-controlled, phase 2 trial	Randomized double-blinded placebo-controlled phase 2 Setting: Nine UK states Follow-up duration: 28 days Primary outcome:Change in condition measured using the WHO 9 point Ordinal Scale for Clinical Improvement during the dosing period [Time Frame: Day 1 to Days 15 and 28] in the ITT population (all participants who received at lease 1 dose of study drug) Secondary outcomes: Change in the Breathlessness, Cough And Sputum Scale (BCSS) score and the safety and tolerability of the investigational drug.	Participants were hospitalised with COVID-19 N = 101 participants (IFN=50, placebo= 51) 101 randomized, 98 analyzed 58 males, 40 females Severity: Mild: n=32, Moderate: n=64, Severe: n=2 Critical: n=0 Placebo: Mean (SD) age at inclusion: 56.5 (11.9) years. Hypertension 11/27 (41%), Chronic lung condition 12/27 (44%), CVD 8/27 (30%), Diabetes 9/27 (33%), Cancer 1/27 (4%) IFN: Mean (SD) age at inclusion: 57 (14.6) years. Hypertension 18/26 (69%), Chronic lung condition 11/26 (42%), CVD 5/36 (19%), Diabetes 3/26 (12%), Cancer 3/36 (12%) Inclusion criteria:1) Positive for SARS-CoV-2 (RT-PCR, or point-of-care viral infection test in the presence of strong clinical suspicion of SARS-CoV-2 infection; 2) Male or female, ≥18 years of age; 3) Admitted to hospital due to the severity of their COVID-19 disease: High temperature and/or new continuous cough, loss or change to sense of smell and/or taste; 4) Provided informed consent; 5) Hospitalised female patients had to be ≥1 year post-menopausal, surgically sterile, or using an acceptable method of contraception.	Nebulised interferon beta-1a (6 MIU in 0.65 mL of solution) Co-Intervention: Standard care. Duration: 14 days Control: Placebo (0.65 mL of solution). Duration: 14 days	48 (intervention) and 50 (placebo) were analysed using the ITT method. 66 (67%) patients required oxygen supplementation at baseline: 29 in the placebo group and 37 in the intervention group. Patients receiving the intervention had greater odds of improvement on the OSCI scale (odds ratio 2·32 [95% CI 1·07–5·04]; p=0·033) on day 15 or 16 and were more likely than those receiving placebo to recover to an OSCI score of 1 (no limitation of activities) during treatment (hazard ratio 2·19 [95% CI 1·03–4·69]; p=0·043). Placebo group, five (10%) patients either underwent intubation or died (OSCI ≥6) between the first dose and day 15 or 16 versus three (6%) in the SNG001 group. No significant difference between treatment groups in the odds of intubation or the time to intubation or death Day 16: 33 (69%) of 48 patients in the placebo group and 35 (73%) of 48 patients in the SNG001 group discharged from hospital By day 28, 39 (81%) of 48 patients discharged in the SNG001 group vs 36 (75%) of 48 in the placebo group. No significant difference between treatment groups in the odds of hospital discharge or time to hospital discharge Treatment emergent adverse event 26 (54%) intervention versus 30 (60%) placebo. The most frequently reported treatment-emergent adverse event was headache (seven [15%] patients in the SNG001 group and five [10%] in the placebo group). Serious treatment emergent adverse events 7 (15%) vs 14 (28%). Most common serious adverse events were related to COVID-19: respiratory failure (three [6%] patients in the SNG001 group *vs*	Risk of Bias 2.0 (www.covid-nma.com), The overall risk of bias reported was **Some concerns** (i) *Randomisation* - Quote: "Patients were randomised to one of two treatment groups (SNG001 or placebo) in a 1:1 ratio according to a prespecified randomisation schedule in addition to standard of care" "Simple randomisation was done manually by use of sealed envelopes, with trained clinical research staff assigning the patient the next available randomisation number on the randomisation list." Comment: Allocation sequence generation not reported. Allocation concealment not fully reported. (ii) *Missing outcome data* - Comment: 101 randomised; 98 analysed. Up to 29% missing data in the intervention group (15/51) and 22% in the control group (11/50) were imputed using the last-observation-carried-forward method. Risk assessed to be some concerns for the outcomes: Mortality. Incidence of clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Time to WHO score 6 and above. Time to WHO score 7 and above. Adverse events. Serious adverse events. *(iii) Selection of the reported results* - Comment: The protocol and statistical analysis plan were available. There were some differences in outcomes measured and reported between the published article, study protocol and trial registry.

		Exclusion criteria:1) Any condition, that in the opinion of the Investigator, constituted a risk or a contraindication for the participation; 2) Current or previous participation in another clinical trial where the patient had received a dose of an Investigational Product containing small molecules within 30 days or 5 half-lives (whichever was longer) prior to entry into this study or containing biologicals within 3 months prior to entry into this study; 3) Ventilated or in intensive care; 4) Inability to use a nebuliser with a mouthpiece; 5) History of hypersensitivity to natural or recombinant IFN-β or to any of the excipients in the drug preparation; 6) Females who were breast-feeding, lactating, pregnant or intending to become pregnant.		six [12%] in the placebo group) and pneumonia (three [6%] *vs* three [6%]). All serious adverse events considered unlikely be related /not related to study treatment. Treatment-related treatment-emergent adverse event: 7(15%) with SNG001 versus 2 (4%) SOC. SNG001 group: Cough in 2 (4%) decreased oxygen saturation (1), diarrhoea (1), dry throat (1), oral pain (1), night sweats (1), tremor (1). There were three deaths in the placebo group and none in the intervention group"	Risk assessed to be low for the outcomes: Mortality. Adverse events. Serious adverse events. Risk assessed to be some concerns for the outcomes: Incidence of clinical improvement. Incidence of WHO score 6 and above (OSCI ≥5). Time to WHO score 6 and above. Incidence of WHO score 7 and above (OSCI ≥6). Time to WHO score 7 and above (OSCI ≥6).
Pan et al (SOLIDARITY), Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results	Randomized controlled trial, Unblinded (1:1) Setting: Multicenter / Multinational (30) Follow-up: 28 days Primary outcome: All-cause mortality, subdivided by the severity of disease at the time of randomization, measured using patient records throughout the study. / In-hospital mortality Secondary outcomes: The initiation of mechanical ventilation and hospitalization duration	N = 4127 participants IFN: n=2063, SOC n= 2064. 11 333 entered the trial, 64 (0.6%) had no consent to follow up leaving 11 266 in the intent-to-treat analysis. N=4127 Age: <50 yr n=3995 (35%), 50-69 yr n= 5125 (45%), ≥70 yr n=2146 (19%) Overall, 81% were younger than 70 years of age, 6985 (62%) were male, 2768 (25%) had diabetes, 2337 (21%) had heart disease, 635 (6%) had chronic lung disease, 529 (5%) had asthma, 15 (%) had chronic liver disease,916 (8%) were already receiving ventilation, and 7002 (62%) underwent randomization on days 0 or 1. Inclusion criteria: Age ≥18 years, hospitalized with a diagnosis of	Remdesivir n =2750, Hydroxychloroquine n=954, lopinavir w/o IFN n=1411, IFN including IFN and lopinavir n =2063, and no drug/control n= 4088 Intervention: Interferon beta-1a (44 mcg). Three doses over 6 days (the day of randomization and days 3 and 6) of 44 µg of subcutaneous interferon beta-1a; where IV interferon was available, patients receiving high-flow oxygen, ventilation, or extracorporeal membrane oxygenation (ECMO) were instead to be given 10 µg	Intention to treat analysis. Deaths were at a median of day 8 (IQR, 4 to 14), and discharges were at a median of day 8 (IQR, 5 to 12). There were 1253 in-hospital deaths (the primary outcome, including those before and after day 28). The Kaplan–Meier risk of in-hospital death to day 28 was 11.8%; a few in-hospital deaths occurred later. This risk was associated with several factors, particularly age (20.4% if ≥70 years and 6.2% if <50 years) and ventilation status (39.0% if the patient was already receiving ventilation and 9.5% otherwise). Death: 243 of 2050 patients receiving interferon and in 216 of 2050 receiving its control (rate ratio, 1.16; 95% CI, 0.96 to 1.39; P = 0.11). Unstratified comparisons yielded similarly null findings, as did analyses that excluded patients receiving glucocorticoids and multivariable sensitivity analyses that estimated trial drug effects simultaneously.	Risk of Bias 2.0 (www.covid-nma.com), The overall risk of bias reported was **Low** *(i) Randomization* - "Trial procedures were minimal but rigorous, with data entry through a cloud-based Good Clinical Practice–compliant clinical data management system that recorded demographic characteristics, respiratory support, coexisting illnesses, and local availability of trial drugs before generating the treatment assignment." Allocation sequence concealed. *(ii) Deviations from intervention* - Comment: Unblinded study (patients and physicians) Antivirals, corticosteroids and biologics were reported and balanced. Data were analyzed using intention-to-treat analysis. *(iii) Missing outcome data* - Comment: 4127 patients randomized, 4100 patients analyzed. Data available for

		COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, and, in the physician's view, with no contra-indication to any study drug. Exclusion criteria: patients without clear consent to follow-up	intravenously daily for 6 days. Control: Standard care Definition of Standard care**:** Local standard of care Duration: 6 days	Ventilation: initiated after randomization in 209 patients receiving interferon and in 210 receiving its control.	>95% of population. Risk assessed to be low for the outcome: Mortality. *(iv) Measurement of the outcome* - Mortality is an observer-reported outcome, not involving judgement. (*v) Selection of the reported results* - The prospective registry and protocol are available. Trial probably analyzed as pre-specified.
Rahmani et al, Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. Department of Pharmacotherapy, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.	Open label randomized controlled trial, unblinded. Setting: Single center/Iran Follow up: 27 days. Primary outcome:In the register: Response to the treatment (according the clinical, paraclinical and laboratory findings); Complications of the treatment (Interview and patient's record). In the report: Time to clinical improvement Secondary outcome: In-hospital complications and 28-day mortality.	N = 80 participants, 40 IFN and 40 standard of care (1:1) Median age (IQR): 60(50-71) 59.09% were male. Severity: Mild: n=0, Moderate: n=65, Severe: n=1 Critical: n=0. No significant difference in terms of the patients' Demographic data was detected between the groups. Common comorbidities: hypertension, diabetes mellitus and ischemic heart disease. Dyspnea, fever and cough were the most frequent symptoms at the time of hospital admission. The median (IQR) time from onset of the symptoms to hospital admission was 7(5–9) and 7(4–8) days in the IFN group and control groups respectively. Inclusion criteria: ≥18 years old with positive PCR and clinical symptoms/signs of pneumonia (including dyspnea, cough and fever), peripheral oxygen saturation (SPO2) ≤ 93% in ambient air or arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) < 300 or SPO2/FiO2 < 315 and lung involvement in chest imaging were included. Exclusion criteria: Serious allergic reactions to IFN, history of suicidal	Intervention: IFN β- 1b (250 mcg subcutaneously every other day for two consecutive weeks) along with the national protocol medications Standard of care: Control group, patients received only the national protocol medications Definition of standard care: The national protocol consisted lopinavir/ ritonavir (400/100 mg BD) or atazanavir/ ritonavir (300/100 mg daily) plus hydroxychloroquine (400 mg BD in first day and then 200 mg BD) for 7–10 days Other supportive care: fluid therapy, stress ulcer prophylaxis, deep vein thrombosis, treatment of electrolyte disorders and antibiotic therapy were considered according to the hospital protocols Duration: 7-10 days	Per protocol/ITT analysis: NR Time to clinical improvement: IFN group was [9(6–10) vs. 11(9–15) days respectively, p = 0.002; HR = 2.30; 95% CI 1.33–3.39. According to the six-category scale, 15.15% and 6.06% of patients were discharged in the IFN and the control groups at day 7 respectively. OR = 2.76; 95% CI: 0.49–15.42, p = 0.21. Day 7: One patient in the control group died at day 7. 2 and 4 patients were intubated in the IFN and control groups respectively. Day 14, percentage of discharged patients was 78.79% and 54.55% in the IFN and control groups respectively (OR = 3.09; 95% CI: 1.05–9.11, p = 0.03). Furthermore, the number of deaths increased to 1 and 3 patients the IFN and control groups respectively." Day 28: proportion of discharged patients - 93.94% in the IFN group and 81.82% in the control group (OR=3.44; 95% CI: 0.64–18.5, p = 0.12). ICU admission rate in the control group was higher than the IFN group (66.66% vs. 42.42%, p = 0.04). The length of hospitalization was shorter [11 (9–13) days in the IFN group vs. 13(10–17) days in the control group p = 0.05] but length of ICU stay was not significantly different between the groups. All-cause 28-day mortality was 6.06% and 18.18% in the IFN and control groups respectively (p = 0.12)"	Risk of Bias 2.0 (www.covid-nma.com), The overall risk of bias reported was **Some concerns** based on *(i) Deviations for intervention* **-** Unblinded study. No participant cross-over. No information on co-interventions of interest, biologics. Administration of antivirals and corticosteroids were reported. Appropriate analysis was used; participants analyzed according to their assigned intervention. *(ii) Measurement of outcome data:* Unblinded study. Mortality is an observer-reported outcome not involving judgement. For WHO score 7 and above, we consider that the assessment cannot possibly be influenced by knowledge of intervention assignment. Risk assessed to be low for the outcome: Mortality. Incidence of WHO score 7 and above. Clinical improvement (defined as at least 2 points improvement on a 6-category scale) and WHO score 6 and above requires clinical judgment and could be affected by knowledge of intervention receipt but are not likely in the context of the pandemic. Risk assessed to be some concerns for the outcomes: Time to clinical improvement. WHO score 6 and above. *(iii) Selection of the reported results:* Neither the protocol nor the statistical analysis plan was available, though the

		thoughts and attempts, alanine amino transferase (ALT) > 5× the upper limit of the normal range, uncontrolled underlying diseases such as neuropsychiatric disorders, thyroid disorders, cardiovascular diseases and also pregnant and lactating women were not included. During the study period, patients who received less than 4 doses of IFN β-1b were excluded.		**Complications IFN vs SOC**: IFN related common adverse effects (injection site reactions 2 (6.06%) and flu-like syndrome 4 (12.12%) occurred only in the IFN group. **Adverse effects IFN vs SOC:** More patients in the control group experienced ARDS 6 (18.18) vs IFN 2 (6.06), secondary infections , septic shock 1 (3.03) vs 4 (12.12), AKI 3 (9.09) vs 4 (12.12) and AHI 2 (6.06) vs 5 (15.15) compared with patients in the IFN group.	authors stated they will include them as supplementary material. The registry was available and utilized. No information on 'time to clinical improvement' was registered but it was reported as an outcome in the paper. Mortality, WHO score 6 and above and WHO score 7 and above outcomes were taken from the "Clinical outcome" endpoint that was registered and then reported in the paper as "Clinical status". However, the timepoints do not correspond. In the registry it is "end of treatment" and in the paper it is "at day 7, 14 and 28". No information on whether the result was selected from multiple outcome measurements or analyses of the data. Trial probably not analyzed as pre-specified. Risk assessed to be some concerns for the outcomes: Time to clinical improvement. Mortality. WHO score 6 and above. WHO score 7 and above.
Davoudi-Monfared, Efficacy and safety of interferon β-1a in treatment of severe COVID-19: A randomized clinical trial Department of Pharmacotherapy, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran.	Open label randomized clinical trial Setting: Hospital in Tehran, Iran Follow up: 4 weeks Primary outcome: time to reach clinical response (days). Clinical response was defined according to the six-category ordinal scale [19]. This scale classifies patients in six categories according to the severity of the viral pneumonia. The six categories are: (1) discharge (2) hospital admission, not requiring oxygen (3) hospital admission, requiring oxygen (4) hospital admission, requiring non-invasive positive pressure ventilation (5) hospital admission requiring	N=92 randomised, 81 analysed- 42 IFN, 39 control. This is reported as due to "drop outs" however 4 died in IFN group during IFN dosing, and 7 dropped out of control arm to join another trial Mean age: 58 yrs 44/81 were male Hypertension (38.3%), cardiovascular diseases (28.4%), diabetes mellitus (27.2%), endocrine disorders (14.8%), and malignancy (11.1%) were common baseline diseases. Inclusion criteria: Adult patients admitted to hospital with severe COVID-19 infection: (1) hypoxemia (need for noninvasive or invasive respiratory support to provide capillary oxygen saturation	Intervention: IFN β-1a in addition to the standard of care:44 micrograms/ml (12 million IU/ml) of interferon β-1a (ReciGen®, CinnaGen Co., Iran) was injected subcutaneously three times weekly for two consecutive weeks. Standard of care: (the hospital protocol) consisted of hydroxychloroquine (400 mg BD in first day and then 200 mg BD) plus lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir	Only the per protocol analysis is presented in the paper. Time to the clinical response was similar in IFN and the control groups (9.7 ± 5.8 vs. 8.3 ± 4.9 days respectively, p=0.95). Investigators reported lower 28-day overall mortality in the IFN group (8 versus 17 deaths). However this excludes 4 deaths, all in the IFN arm, which were omitted from the analysis. These deaths occurred during interferon dosing; 2 had received 1 dose, and 2, 2 doses of interferon. When these deaths are included in an ITT, there are 12 deaths in the interferon group and 17 in the control group, RR 0.71 (95% CI 0.38 to 1.31) Investigators report that "Early administration (<10 days after symptom onset) significantly reduced mortality (OR=13.5; 95% CI: 1.5-118). However, late administration of	Risk of Bias 2.0 (www.covid-nma.com) The overall risk of bias reported was **High** Based on missing outcome data: 92 randomized/81 analysed. Four patients in the intervention arm were excluded because they died before finishing the first week treatment (i.e., received <3 doses of IFN). The reason for missing data is associated with the outcome for mortality, time to clinical improvement and WHO clinical progression scale outcomes (estimated using an ordinal scale that takes death into account). Seven patients in the control arm were excluded because the left the study to enter another trial. Risk assessed to be high for the outcomes: Mortality. Time to clinical improvement. WHO clinical progression

	invasive mechanical ventilation (6) death. Time to clinical response was considered days required to at least two scores improvement in the scale or patient's discharge, which one that occurred sooner. Secondary outcomes: Duration of mechanical ventilation, duration of hospital stay, length of ICU stay, 28-day mortality, effect of early or late (before or after 10 days of onset of the symptoms) administration of IFN on mortality, adverse effects and complications during the hospitalization. The Naranjo scale was used for evaluation of adverse effects of IFN.	above 90%) (2) Hypotension (systolic blood pressure less than 90 mmHg or vasopressor requirement) (3) renal failure secondary to COVID-19 (according to KDIGO definition) (4) neurologic disorder secondary to COVID-19 (decrease of 2 or more scores in Glasgow Coma Scale) (5) thrombocytopenia secondary to COVID-19 (platelet count less than 150000 /mm3) (6) severe gastrointestinal symptoms secondary to COVID-19 (vomiting/diarrhea that caused at least mild dehydration). Exclusion criteria: allergy to IFNs, receiving IFNs for any other reasons, previous suicide attempts, alanine amino transferase (ALT) > 5× the upper limit of the normal range and pregnant women.	(300/100 mg daily) for 7-10 days. Also primary care, respiratory support, fluid, electrolytes, analgesic, antipyretic, corticosteroid and antibiotic were recommended in the hospital protocol if indicated. 26 (62%) of interferon and 15 (44%) of control participants received corticosteroids.	INF did not show significant effect (OR=2.1; 95% CI: 0.48-9.6)." It is unclear how this analysis was performed, and how participants receiving IFN 10 days after symptom onset were categorised. On day 14, 67% vs. 44% of patients in the IFN group and the control group were discharged, respectively (OR= 2.5; 95% CI: 1.05- 6.37). NOTE: this is not specified as an endpoint in the methods Duration of mechanical ventilation was similar(days ± SD) IFN 10.86 ± 5.38 vs 7.82 ± 7.84 , p=0.47 Length of hospital stay (days ± SD) was similar IFN 14.80 ± 8.45 vs 12.25 ± 7.48, p= 0.69 Length of ICU stay (days ± SD) was similar IFN 7.71 ± 8.75 vs 8.52 ± 7.48, p=0.42 **Complications IFN vs SOC:** Acute kidney injury 12 (29%) vs 11 (28%), p=0.58 Nosocomial infections 11 (26%) vs 5 (13%) p=0.09 Septic shock 10 (24%) vs 7 (18%), p=0.35 Hepatic failure 5 (12%) vs 9 (23%), p=0.15 DVT 1 (2%) vs 0, p=0.51 **Adverse effects** IFN vs SOC: By ITT, RR for adverse effect 14 (95% CI 1.92 to 102.13) Hypersensitivity reactions 1 (2%) vs 0 p=0.51 IFN-related injection reactions 8(19%) vs 0 Neuropsychiatric problems 4 (10%) vs 0 p=0.06 Indirect hyperbilirubinemia 1 (2%) vs 1 (3%) p= 0.73	scale score 6 and above. WHO clinical progression scale score 7 and above. There were also concerns with the reporting on randomisation and allocation concealment, lack of blinding and unclear risk of selective outcome reporting (no protocol was available).

Table 2. List of planned and ongoing studies (source: www.covid-nma.com 18 March 2021)

Treatment (per arm)	Sample size	Severity at enrollment	Sponsor/Funder	Reg. number
(1) Umifenovir vs (2) Umifenovir + interferon alpha	100	Moderate/severe	Tongji Hospital	NCT04254874
(1) Chloroquine vs (2) Hydroxychloroquine vs (3) Remdesivir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care	1000	Moderate/severe/critical	Vilnius University Hospital Santaros Klinikos	EUCTR2020-001366-11-LT
(1) Interferon alpha vs (2) Recombinant super-compound interferon (rSIFN-co)	100	Moderate/severe	West China Hospital, Sichuan University	ChiCTR2000029638
(1) Antiviral therapy + TCM vs (2) Antiviral therapy + TCM + interferon alpha2b vs (3) Antiviral therapy + TCM vs (4) Antiviral therapy + TCM + interferon alpha2b	480	Moderate/severe	The First Affiliated Hospital of Medical College of Zhejiang University	ChiCTR2000029573
(1) Interferon beta 1a vs (2) Placebo	100	Mild/moderate	CinnaGen company	IRCT20200511047396N1
(1) Interferon alpha vs (2) Interferon beta vs (3) Placebo	76	No restriction on type of patients	Mashhad University of Medical Sciences	IRCT20161206031256N3
(1) Hydroxychloroquine vs (2) Hydroxychloroquine + raltegravir vs (3) Hydroxychloroquine + interferon beta + raltegravir	60	Severe	Jahrom University of Medical Sciences	IRCT20200412047042N1
(1) Interferon alpha2b vs (2) Lopinavir + ritonavir vs (3) Lopinavir + ritonavir + interferon alpha2b	90	No restriction on type of patients	The First Hospital of Changsha; The Second Xiangya Hospital of Central South University	ChiCTR2000029496
(1) Interferon alpha1b + ribavirin vs (2) Lopinavir + ritonavir + interferon alpha1b vs (3) Lopinavir + ritonavir + ribavirin + interferon beta1	108	Mild/moderate	Chongqing Public Health Medical Center	ChiCTR2000029387
(1) Interferon beta 1a vs (2) Standard of care	126	Moderate/severe	IRCCS San Raffaele	NCT04449380
(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Interferon beta 1a vs (4) Dexamethasone vs (5) Placebo	2500	Moderate/severe/critical	University of Oxford	EUCTR-2020-001113-21-GB
(1) Hydroxychloroquine vs (2) Remdesivir vs (3) Lopinavir + ritonavir vs (4) Lopinavir + ritonavir + interferon beta1 vs (5) Standard of care	3100	Moderate/severe/critical	Institut National de la Sant© Et de la Recherche M©dicale, France	NCT04315948
(1) Hydroxychloroquine vs (2) Lopinavir + ritonavir vs (3) Lopinavir + ritonavir + interferon beta1 vs (4) Remdesivir vs (5) Standard of care	800	Severe	Gesundheit Nord gGmbH	EUCTR2020-001549-38-DE
(1) Interferon beta-1b + clofazimine vs (2) Clofazimine vs (3) Standard of care	81	No restriction on type of patients	The University of Hong Kong	NCT04465695
(1) Umifenovir + interferon alpha vs (2) Umifenovir + interferon alpha + bromhexine	60	Mild	Second Affiliated Hospital of Wenzhou Medical University	NCT04273763
(1) Type 1 interferon vs (2) Placebo	60	Moderate/severe/critical	Centre Hospitalier Universitaire, Amiens	NCT04469491
(1) Lopinavir + ritonavir + ribavirin + interferon beta1 vs (2) Lopinavir + ritonavir	70	Mild/moderate	The University of Hong Kong	NCT04276688
(1) Xiyanping injection + Lopinavir/ritonavir + alpha-interferon nebulization vs (2) Lopinavir + ritonavir + interferon alpha	348	Mild/moderate	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	NCT04275388
(1) Interferon alpha2b vs (2) Standard of care	40	Moderate	Cadila Healthcare Limited	NCT04480138
(1) Interferon vs (2) Standard of care	60	Severe/critical	Ghoum University of Medical Sciences	IRCT20160118026097N3
(1) Interferon beta-1a + remdesivir vs (2) Remdesivir	1038	Moderate/severe/critical	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04492475
(1) Interferon beta 1a vs (2) Standard of care	30	No restriction on type of patients	Tehran University of Medical Sciences	IRCT20100228003449N28
(1) Interferon beta-1b + ribavirin vs (2) Standard of care	96	Moderate/severe/critical	The University of Hong Kong	NCT04494399
(1) Interferon beta 1a vs (2) Standard of care	30	No restriction on type of patients	Tehran University of Medical Sciences	IRCT20100228003449N27
(1) Interferon alpha2a + ribavirin vs (2) Umifenovir + ribavirin	30	Mild/moderate	Foshan First People's Hospital	ChiCTR2000030922
(1) Favipiravir + interferon beta 1a vs (2) Lopinavir + ritonavir + interferon beta 1a	60	Moderate	Bandare-abbas University of Medical Sciences	IRCT20200506047323N3

Appendix 1: Search strategy

Date for the updated review: 1 March 2021

Database: Cochrane COVID-19 Study Register

Search Strategy: Interferon OR interferons; filtered by: Intervention assignment = Randomised

Date searched: 1 May 2020 – 1 March 2021

Number of studies: 79 studies (137 records) – imported 114 (23 duplicates)

Database: LOVE (Living Overview of Evidence) PLATFORM

Search terms: Interferon OR interferons; filtered by Publication type = Prevention or treatment and Type of study = RCT

Records retrieved: 73 randomised trials – imported 28 (45 duplicates)

Database: LOVE (Living Overview of Evidence) PLATFORM

Search terms: Interferon OR interferons; filtered by Publication type = Prevention or treatment

Records retrieved: 34 systematic reviews (imported 30 (4 duplicates)

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: ☐ Small: ☐ None: ☒ Uncertain: ☐	Mortality was 12.9% (243/2050) in the interferon arm versus 11.0% (216/2050) in the standard of care arm, rate ratio for death 1.16 (95% confidence interval 0.96 to 1.39); there may be 17 more deaths per 1000 people treated with interferon compared to no treatment (ranging from 4 fewer to 41 more deaths).
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: ☐ Small: ☐ Uncertain: ☒	Largest study (Pan et al) did not report on safety.
BENEFITS & HARMS	**Do desirable effects outweigh undesirable harms?** Favours intervention: ☐ Favours control: ☒ Intervention = Control *or* Uncertain: ☐	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High: ☐ Moderate: ☐ Low: ☒ Very low: ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	The results are GRADE as low to moderate for all critical outcomes.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: ☐ No: ☐ Uncertain: ☒	SAHPRA-registered products: Rebif 22 (INF-β1a), Rebif 44 (INF-β1a), Pegasys (pegINF-α2a), Intron A 10 miu (INF-α-2b), Avonex (INF-β1a), Plegridy (pegINF-α2a), Betaferon (INF-β1b). *Note:* Intron A is not marketed locally, may be accessed via S21 from relevant countries; Available stock currently covers MS indication.
RESOURCE USE	**How large are the resource requirements?** More intensive: ☒ Less intensive: ☐ Uncertain: ☐	**Price of medicines:** **Medicine (pack size), Trade name®** / **Tender price*** / **SEP**** INF-β1a, 30mcg/ml (4), Avonex® / R4547.54 / R7640.00 INF-β1b, 0.25mg/ml (1), Betaferon® / R418.64 / R506.67 INF-β1a, 44mcg/ml (12), Rebif 22® / n/a / R6859.67 INF-β1a, 88mcg/ml (12), Rebif 44® / n/a / R7641.67 *Contract circular HP04-2020ONC [Accessed 18 March 2021] ** SEP database, 28 December 2020
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: ☐ Major: ☒ Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: ☐ No: ☐ Uncertain: ☒	No data on this. No data about acceptability.
EQUITY	**Would there be an impact on health inequity?** Yes: ☐ No: ☐ Uncertain: ☒	This would depend on access and capacity to deliver the intervention to all who need it. We have not data on this.

Appendix 3: Updating of a rapid report

Date	Signal	Rationale
9 December 2020	New efficacy signal	Previous report described evidence of safety and efficacy that was very uncertain. The WHO SOLIDARITY RCT results have recently been published in the NEJM.