Should Interferon be used in the treatment of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of Interferon in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

Currently, there is insufficient evidence to conclude on the efficacy and safety of interferons (IFNs) in the treatment of COVID-19

- Interferons (IFNs) are important innate antiviral cytokines making the cells refractory to virus replication. Currently it is being used in the treatment of Chronic Hepatis B and C, cutaneous melanoma and multiple sclerosis [1-5].
- There is an unpublished *in vitro* study which demonstrated potent efficacy of human Type I IFN (IFN I) in suppressing SARS-CoV-2 infection in Vero cells [15]. Published *in vitro* studies from SARS-CoV and MERS-CoV suggest that IFN-β, PEG INF as well as IFN-α may be used for treatment. The timing of administration should be prior to infection and early post-infection [6-9]
- There are 2 retrospective studies done. One is a cohort of children with mild to moderate COVID-19 infection which were given IFN-α by aerosolization with or without lopinavir-ritonavir. Results showed improvement in pneumonia by 4–10 days after treatment initiation. SARS-CoV-2 RT-PCR results became negative after a mean of 10 days of treatment and the mean number of days in hospital was 14 days [16]. The second is a cohort of adults with moderate COVID-19 infection given IFN-α2b by nebulization with or without aribidol, results showed reduction of the duration of detectable COVID-19 in the upper respiratory tract and in parallel reduced the duration of elevated blood levels for the inflammatory markers, IL 6 and CRP [17].
- Currently, there is no completed clinical trial on the efficacy of interferons as treatment for COVID-19.
- However, there are 5 ongoing clinical trials being conducted in several countries [18-23]
- The COVID-19 Clinical Practice Guidelines (2020) of the Medical and Health Care Wuhan University Novel Coronavirus Management & Research Team and China International Exchange & Promotive Association has recommended giving IFN-α atomization inhalation at a dose of 5 million U/treatment in sterile injection water, twice daily as treatment [24].

RESULTS

Up to the present time, there are no completed randomized clinical trials on the efficacy of interferons as treatment for patients with COVID-19. However, we found 1 unpublished *in vitro* study [15], one published retrospective cohort study [16], and 1 unpublished retrospective cohort [17]; the 2 cohort studies were done in China. There are 5 ongoing trials and the characteristics of these studies are summarized in Appendix 1.

In an unpublished *in vitro* study, result indicated that IFN-α treatment potently inhibited SARS-CoV-2 infection. Virus titers were not detectable except at the lowest concentration tested (50 IU/ml), at which the viral titers were drastically reduced by 4 logs of magnitude. For IFN-β, the virus titers were below the detection limit at all concentrations tested (50 u/ml-1000u/ml), indicating more potent anti-SARS-CoV-2 activity than IFN-α. These results showed that IFN I demonstrated potent efficacy in suppressing SARS-CoV 2 infection in Vero cells, a finding which could inform future treatment options for COVID-19. [15].

A published retrospective cohort of 36 children with mild to moderate COVID-19 infection all were given IFN-α by aerosolization twice a day, fourteen of which (39%) received lopinavir–ritonavir syrup twice a day, and six (17%) needed oxygen inhalation. In the 13 patients with fever, mean duration of fever was 3 days. Improvement in pneumonia was seen 4–10 days after treatment initiation. SARS-CoV-2 RT-PCR results became negative after a mean of 10 days of treatment, regardless of the various initial manifestations of patients. The mean number of days in hospital was 14 days. All patients were cured, according to the criteria for cured outcome, and quarantined for a further 2 weeks [16] Although all of the children in the cohort was cured regardless if they took IFN alone or in combination with lopinavir-ritonavir, the efficacy of IFN remains unclear, because all of the participants in the cohort were children and based on observational studies, children have better prognosis than adults.

The unpublished retrospective cohort of adult patients with moderate COVID-19 infection received antiviral treatment with either IFN-α2b (Tianjin Sinobloway Biology, 5mIU/ml) by nebulization, arbidol (ARB) (arbidol hydrochloride; Jiangsu Simcere Pharm. Co.,100mg dispersible tablets), or a combination of IFN-α2b plus ARB, results showed that irrespective of the treatment group, none of the patients evaluated in the study exhibited persistent signs or symptoms of end organ dysfunction. Specifically, none of the patients developed respiratory distress requiring prolonged oxygen supplementation or intubation; consequently, none of the patients in the cohort required intensive care. The study found that age, sex and co-morbidities has no effect on disease course or laboratory measurements. In terms of viral clearance, treatment with IFN-α2b with or without arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel reduced duration of elevated blood levels for the inflammatory markers, IL 6 and CRP. The findings suggest that IFN-α2b should be further investigated as a therapy in COVID-19 cases [17]

Currently, the WHO does not recommend any specific anti-viral agent against COVID-19 [24]. However, Chinese guidelines recommend the nebulization of interferon alpha at a dose of 5 million U/treatment in sterile injection water, twice daily, as one of the anti-viral options for COVID – 19 [23].

CONCLUSION

There are 2 retrospective cohort studies and 1 *in vitro* study which shows possible beneficial effect of giving IFN I to COVID-19 infection but since these studies are considered low quality evidence in proving efficacy of treatment. A randomized controlled trial is warranted before it can be recommended as part of the treatment regimen for COVID-19 patients.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Montalo Emily, Bukreyeva N. Maruyama J. Passler S. Huang C	*In vitro* study		Vero Cells infected with COVID-19	Type 1 Interferon	Without interferon	Viral titers	treatment with low concentrations of both IFN-α and IFN-β significantly inhibited viral infection, with IFN-β being slightly more effective than IFN-α
2	Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D.	Retrospective cohort	China	Children with Mild to moderate C)VID-19	Interferon-β and mycophenolic acid	lopinavir–ritonavir	lopinavir–ritonavir + lopinavir–ritonavir	All patients were cured
3	Zhou Q. Wei X. Xiang X. Wang X. Wang Z. Chen V. Shannon C. Tebbutt S. Kollmann T. Fish E	Retrospective cohort	China	Laboratory confirmed COVID-19 patients	IFN-α2b Arbidol IFN-α2b + Arbidol		Time-to-viral clearance	

Table 2. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04331899 A Phase 2 Randomized, Open Label Study of a Single Dose of Peginterferon Lambda-1a Compared With Placebo in Outpatients With Mild COVID-19	Not yet recruiting	April 15, 2020-May 31, 2021	open-label randomized controlled trial	Not provided	- Age ≥ 18 years and ≤ 64 years - Initial diagnosis of COVID-19 disease as defined by a FDA-cleared molecular diagnostic assay positive for SARS-CoV-2 - symptoms of COVID respiratory infection without respiratory distress	Peginterferon Lambda-1a + Standard of care	Standard of care	Duration of Viral shedding of SARS-CoV-2 by qRT-PCR [Time Frame: 28 days]
2	NCT04293887 Randomized, open, blank controlled trial for the efficacy and safety of recombinant human interferon alpha 1beta in the treatment of Wuhan patients with novel coronavirus pneumonia (COVID-19)	Not yet recruiting	March 1, 2020 - May 30, 2020	multi-center, randomized, open, blank-controlled, multi-stage clinical study	Not provided	-Aged >=18 years; -Clinically diagnosed patients with COVID-19, including: on the basis of meeting the criteria for suspected cases, one of the following etiology evidence: (1) real-time fluorescent RT-	Standard treatment + recombinant human interferon α1β 10ug Bid was administered by nebulization for 10 days.	Standard therapy + blank therapy	The incidence of side effects dyspnea SPO2≤94% respiratory rate ≥24

						PCR detection of SARS-Cov-2 nucleic acid samples in respiratory or blood samples; (2) Sequencing of viral genes in respiratory specimens or blood specimens, highly homologous to known SARS-Cov-2; -The interval between the onset of symptoms and random enrollment is within 7 days. The onset of symptoms is mainly based on fever. Cough, diarrhea or other related symptoms can be used for the evidence of onset symptoms if without fever.			breaths/min in oxygen state) [Time Frame: Within 14 days after enrollment]
3	ChiCTR2000029989 A randomized controlled Trial for therapeutic efficacy of Recombinant Human Interferon alpha 1b Eye Drops in the treatment of elderly with novel coronavirus pneumonia (COVID-19)	Not yet recruiting	February 02, 2020 To April 31, 2020	Randomized controlled Trial	China	-Aged >=60 years; -Patients confirmed with novel coronavirus pneumonia. The Diagnostic criteria refer to "Pneumonitis Diagnosis and Treatment Scheme for Novel Coronavirus Infection; - Those without broad-spectrum antibacterial, antifungal, and antiviral treatment; - Imaging revealed pneumonia in patients with a diagnosis of pathogen: influenza, CAP/HAP bacterial infection, and fungal infection;	Recombinant Human Interferon α1b Eye Drops	placebo drop	Clinical symptoms

						- Participants signed informed consent before the study; - It must be agreed not to participate in other clinical studies until the 28th day of completion.			
4	2EUCTR2020-001023-14-GB A randomised double-blind placebo-controlled trial to determine the safety and efficacy of inhaled SNG001 (IFNβ-1a for nebulisation) for the treatment of patients with confirmed SARS-CoV-2 infection (COVID-19)	Ongoing	March 17, 2020	Randomized double-blind placebo-controlled trial	United Kingdom	- Positive virus test for SARS-CoV-2 - Male or female, ≥18 years of age at the time of consent - Patients admitted to hospital due to the severity of their COVID-19 disease OR non-hospitalised patients from high-risk co-morbidity groups such as the >65-years of age, or those with hypertension, cardiovascular disease, diabetes or a chronic lung condition	Interferon beat-1a (IFN-β1a) inhalation	Nebulization Solution	Change in condition measured using the Ordinal Scale for Clinical mprovement during the dosing period. The Ordinal Scale for Clinical Improvement is a World Health Organisation recommended scale for use in COVID-19 trials.
5	IRCT20100228003449N28 Evaluating efficacy and safety of interferone ß-1a in the treatment COVID-19 infection	recruiting	March 15, 2020-	randomized open-label placebo-controlled trial	Iran	Patients with highly suspected or confirmed COVID-19 infection who are candid for hospitalized and starting triple-drug combination	Concomitant with the national corona treatment recommendation (hydroxychloroquine + Oseltamivir +Lopinavir/ritonavir), patients will receive interferon B, sub type 1a (CinnaGen Company) with dose of 44 mcg subcutaneously every other day for 14 days.	Patients will receive the national corona treatment recommendation (hydroxychloroquine + Oseltamivir +Lopinavir/ritonavir) for at least 5 days.	Complications of the treatment. Timepoint: Daily. Method of measurement: Interview and patient's record. Response to the treatment. Timepoint: Daily. Method of measurement: According the clinical, paraclinical and laboratory findings.