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Original Article

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Effects of Interferon Beta in COVID-19 adult patients: Systematic Review

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ABSTRACT

Background: The high rate of transmission and infection of coronavirus disease 2019 (COVID-19) is a public health emergency of major epidemiological concern. No definitive treatments have been established, and vaccinations have only recently begun. We aim to review the efficacy and safety of Interferon Beta (IFN-β) in patients who have a confirmed COVID-19 diagnosis.
Materials and Methods: A search from PubMed, Science Direct, Cochrane, and Clinicaltrials.gov databases were conducted from December 2019 to December 2020 to review the efficacy and safety of IFN-β in adult patients with COVID-19 confirmed. We included randomized controlled trials, case reports, and experimental studies. Correspondences, letters, editorials, reviews, commentaries, case control, cross-sectional, and cohort studies that did not include any new clinical data were excluded.
Results: Of the 66 searched studies, 8 were included in our review. These studies demonstrated that although IFN-β did not reduce the time to clinical response, there was an increase in discharge rate at day 14 and a decrease in mortality at day 28. The time to negative reverse transcription polymerase chain reaction (RT-PCR) was shown to be significantly shortened in patients receiving IFN-β, along with a lower nasopharyngeal viral load.Further, patients receiving IFN-β had a less significant rise in IL-6. IFN-β was shown to decrease intensive care unit (ICU) admission rate, the requirement of invasive ventilation in severe cases, and improve the survival rate compared to control groups. There were no severe adverse events reported.Our review found that patients who received early treatment with IFN-β experienced significantly reduced length of hospitalization, mortality, ICU admission, and mechanical ventilation. A greater chance of clinical improvement and improved imaging studies was noted in patients who received IFN-β. There were no reported deaths associated with the addition of IFN-β. Further randomized trials involving more significant sample sizes are needed to better understand the effect of IFN-β on survival in COVID-19.
Conclusion: This review identified encouraging data and outcomes of incorporating IFN-β to treat COVID-19 patients. IFN-β has been shown to decrease hospital stay's overall length and decrease the severity of respiratory symptoms when added to the standard of care. Also,

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Conflict of Interest
No conflicts of interest.

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in some studies, it has been demonstrated to reduce the length of ICU stay, enhance survival rate, and decrease the need for invasive mechanical ventilation. There were minor side effects reported (neuropsychiatric symptoms and hypersensitivity reaction). However, randomized clinical trials with a large sample size are needed to assess IFN-β's benefit precisely.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Interferon beta; Beta-Interferon

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has become a worldwide threat since it emerged in December 2019. As per the World Health Organization (WHO), the global number of confirmed cases of COVID-19 was 98.2 million, including over 2.1 million deaths as of January 27, 2021 [1]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a single-stranded positive-sense RNA (+ssRNA) virus belonging to the beta-coronaviruses, similar to SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. There are four structural proteins on the SARS-CoV-2 virion (spike, envelope, membrane, and nucleocapsid) 19 [3, 4]. SARS-CoV-2 enters the host cell through the attachment of the spike glycoprotein of the virion to the angiotensin-converting enzyme 2 receptors of the host cell [3, 4]. To date, no definitive treatment has been established, so efficacious treatments to combat this novel disease are desperately needed and are being investigated globally in an accelerated manner [5-8].

IFN-β is a cytokine produced by mammalian cells, and IFN-β 1b is produced in modified *Escherichia coli* [9]. Based on protein structures and cell-surface receptors, interferons are divided into type I interferons (alpha, beta, epsilon, kappa and omega subtypes), type II interferons (gamma subtype), and type III interferons (lambda subtypes) [8]. They are expressed early on in the host defense mechanism against multiple viruses [8]. The coronavirus is a weak inducer for interferon and cannot activate the body defense mechanism, but cell culture and animal experiments with interferons show that it can inhibit coronaviruses' replication [8]. Therefore, interferon therapy could be considered a substitute for our weakened immune system against the coronavirus [8].

IFN-β has been used to treat multiple sclerosis through the downregulation of the major histocompatibility complex (MHC) class II expression in antigen-presenting cells, the induction of IL-10 secretion, and the inhibition of T-cell migration [10]. It is a broad-spectrum antiviral agent which inhibits viral replication through interactions with toll-like receptors [11]. Existing studies on the efficacy of treatments for SARS-CoV and the MERS-CoV provide insight into these drugs' potential repurposing for SARS-CoV-2 treatment. Studies have reported IFN-β to have anti-SARS-CoV activity in vitro and potent activity in reducing MERS-CoV replication (EC_{50} = 1.37 - 17 IU/mL) [11]. Further, SARS-CoV-2 was more susceptible and sensitive to type I interferons than SARS-CoV [12].

Once the human body is exposed to chemicals or biological stimuli, IFN-β starts producing by the immune system [13]. It has multiple functions on diverse cells of the human body, including antiviral, anti-inflammatory, and activation of the immune system [14]. Viral infection triggers the initiation of interferon-stimulated genes (ISGs) and this strikes viral cell cycles [14].

According to the study, it shows that amongst the interferon family, IFN-β has a high binding affinity for gene expression as it is directly involved in the upregulation of inflammatory agents by the molecular expression, and in the same manner, its declines in pro-inflammatory cytokines [15]. One of the properties of beta interferon is the expression of protein CD-73, which reduces lung vascular permeability and improves acute respiratory distress syndrome (ARDS) [16]. The antiviral and immunomodulatory effects of IFN-β could be most effective if used in the early stages of COVID-19, and IFN-β-1a could be safe to use also in ARDS [17, 18].

To date, there are no definitive treatments established for COVID-19, and vaccination has just recently begun. We aim to perform a systematic review of IFN-β's efficacy and safety in patients with a SARS-CoV-2 diagnosis.

MATERIALS AND METHODS

A database search of PubMed, ScienceDirect, Cochrane, and Clinicaltrials.gov was performed, including articles from December 2019 to December 2020, to review IFN-β's efficacy and safety in patients confirmed with SARS-CoV-2. The MeSH terms 'COVID-19', 'Coronavirus', 'SARS-CoV-2', 'Interferon beta', 'beta interferon', 'Interferon-beta' were used (**Table 1**). Articles reporting COVID-19 confirmed patients (age 18 years or older) being treated with interferon were included in the analysis. The outcomes of safety, tolerability, and treatment effectiveness were extracted. All randomized controlled trials, case-report, and experimental studies were included. Articles were eligible following these criteria; however, they may be excluded if appropriate information was not reported. We also excluded correspondences, letters, editorials, reviews, commentaries, case control, cross-sectional, and cohort studies that did not include any new clinical data.

1. Selection of studies

All articles were retrieved by two authors (MF, MB) and had no language barriers, and were filtered out for duplications. We included articles with these design types (randomized

Table 1. Search methods for identification of studies

Population	Intervention	Comparison	Outcome
COVID-19	Interferon beta	Control	Efficacy and Safety
(((COVID-19[Title]) OR (SARS-CoV-2 [Title]) OR (Coronavirus)))	(((Interferon beta [Title]) OR (beta Interferon [Title])) OR (Interferon-beta [Title]))		Efficacy [All Fields]
· 2019 novel coronavirus disease · COVID19 · COVID-19 pandemic · SARS-CoV-2 infection · COVID-19 virus disease · 2019 novel coronavirus infection · 2019-nCoV infection · coronavirus disease 2019 · coronavirus disease-19 · 2019-nCoV disease · COVID-19 virus infection	· Interferon beta · Interferon, Fibroblast · Fibroblast Interferon · Interferon, beta · beta Interferon · beta-Interferon · Fiblaferon · beta-1 Interferon · beta 1 Interferon · Interferon-beta1 · Interferon beta1 · Interferon, beta-1 · Interferon, beta 1		· Outcome, Treatment · Patient-Relevant Outcome · Outcome, Patient-Relevant · Outcomes, Patient-Relevant · Patient Relevant Outcome · Patient-Relevant Outcomes · Clinical Effectiveness · Effectiveness, Clinical · Treatment Effectiveness · Effectiveness, Treatment · Rehabilitation Outcome · Outcome, Rehabilitation · Treatment Efficacy · Efficacy, Treatment · Clinical Efficacy · Efficacy, Clinical

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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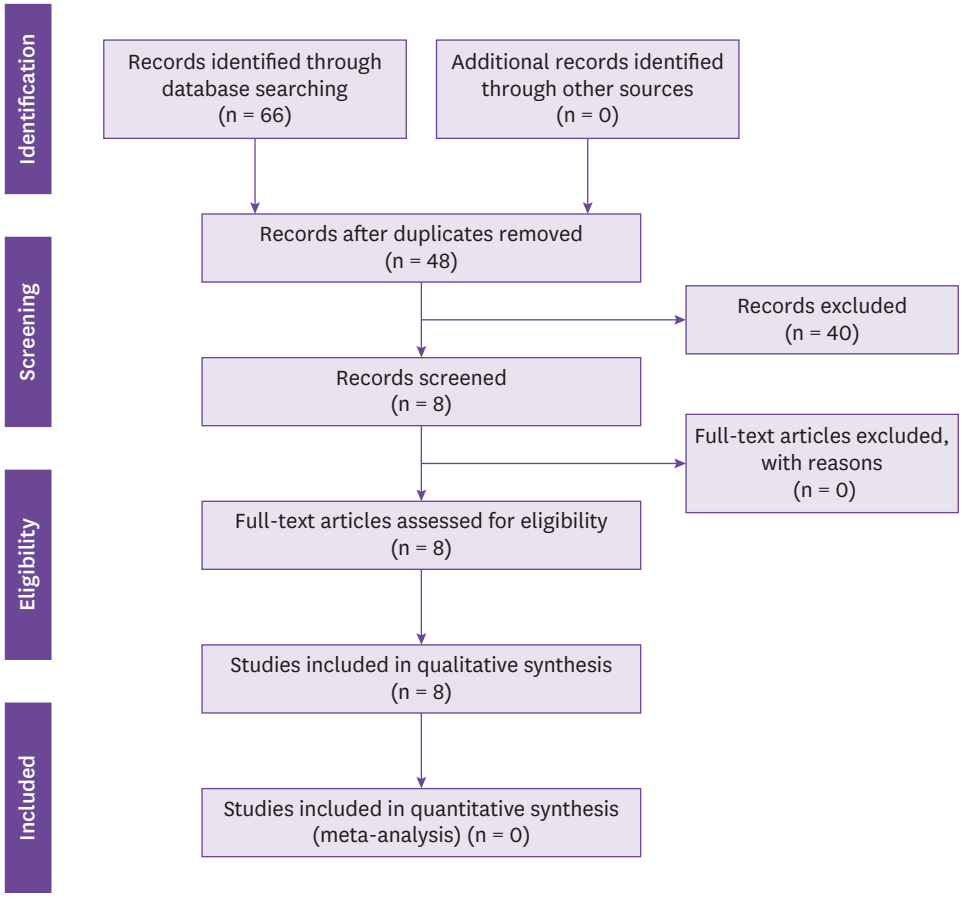

Figure 1. PRISMA flowchart [31].

controlled trials, case-reports) and reviewed the abstract of potentially relevant studies. Among those articles that were duplicated, we considered maintaining just the first one. We avoided those studies that did not follow the election criteria (for example, those that associated the drug with other diseases). On the other hand, we acquired the full-text article of those remaining who fulfilled the eligibility criteria. Investigators were not blinded during searching and selecting information, so complete authors' names were visible for them, subtracting the study's value. Nonetheless, we followed this path towards expediting the time of completion of the paper. It is worth mentioning that all the selected studies were chosen unanimously. Of the 66 searched studies, 8 were included in our review (**Fig. 1**, **Table 2**).

2. Data extraction and management

Two review authors extracted those crucial data, including participants, methods, interventions, outcomes, and results. We split the relevant information into the following topics below:

- Characteristics of the study: first author name, year of publication, and place of study.
- Study design: sample size, type of study.
- Population characteristics: age, sex, demographic, comorbidities.
- Type of intervention: doses, interval time, administration route (inhaled or subcutaneous [SC]), timing, combination regimen and treatment period.
- Primary Outcomes: efficacy, safety, and tolerability.

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Table 2. Included studies and characteristics

Study No.	Author	No. of participants	Duration of Study	Intervention	Results
1	Davoudi-Monfared E, et al. (2020) [16] Randomized Clinical Trial.	92	2 weeks	Treatment group-IFN-β 1a 44-μg/ml s/c injection 3 × /week for 2 weeks + National protocol medications Control group-Standard of Care	Early administration significantly reduced mortality (OR, 13.5; 95% CI, 1.5 to 118). Although IFN did not change the time to reach the clinical response, adding it significantly increased discharge rate on day 14 and decreased 28-day mortality. No adverse events reported in either group.
2	Rahmani H, et al. 2020 [24] Randomized Clinical Trial.	72	2 weeks	Treatment group- IFN β-1b 250 μg subcutaneously every other day, subcutaneously & National Protocol medications. The Control group: only National protocol medicines; which is: HCQ (Day 1 400 mg/BID followed by 200 mg P.O BID) for 7 days and lopinavir/ritonavir (200/50 mg po, two tablets QID) for 5 days.	IFN β-1b was effective in shortening the time to clinical improvement. No adverse events. ICU admission rate and need for invasive mechanical ventilation significantly reduced by administration of IFN β-1b. Compared with the control group, IFN β-1b reduced the duration of hospitalization. (78.79% *vs.* 54.55%) mortality (6.06% *vs.* 18.18%) No significant difference in length of ICU stay, intubation rate and 28-day mortality. benefit of IFN β-1b.
3	Dastan F, Nadji SA, et al 2020 [22] Prospective Non-Controlled Clinical Trial.	20	March 2020	20 patients included. They received IFN-β-1a at a dose of 44 μg subcutaneously every other day up to 10 days. All patients received conventional therapy including HCQ 200 mg P.O BID and lopinavir/ritonavir (200 mg po/50 mg po two tablets QID × 5 days.	Fever resolved in all patients during the first seven days. Virological clearance showed a significant decrease within 10 days. Imaging studies showed significant recovery after a 14-day period in all patients. The mean time of hospitalization was 16.8 days. There were no deaths or significant drug reactions in the 14-day period. Findings supported the use of IFN-β 1a in combination with HCQ and lopinavir/ritonavir in the management of COVID-19.
4	Hung IF, Lung, et al 2020 [20] Multicenter, Prospective Randomized clinical trial: Phase 2	168	6 weeks	86 patients in the intervention group and 41 patients in the control group. Within the combination group, 52 patients were admitted to the hospital less than 7 days from symptom onset and received the lopinavir-ritonavir, ribavirin, and interferon beta-1b regimen, and 34 patients who were admitted 7 days or more after symptom onset received the lopinavir-ritonavir and ribavirin only regimen. The median number of days from symptom onset to start of study treatment was 5 days. Patients were randomly assigned to a 14 day combination of lopinavir 400 mg po and ritonavir 100 mg po every 12 hr, ribavirin 400 mg every 12 hour and three doses of 8 million IU of IFN-β ib Subcutaneous on alternate days (combination group) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 hour (control group)	The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days) than the control group (12 days) hazard ratio:4.37, $P = 0.0010$. Adverse events were not different between the groups. One patient in the control group discontinued because of biochemical hepatitis. No deaths. The study didn't provide any information on the cost effectiveness of interferon beta
5	Khamis.F and Naabi HA et al.2020 [21] Randomized Clinical Trial	89	June 22, 2020 to August 13, 2020.	Favipiravir with inhaled IFN-β assigned to n = 44 & HCQ assigned to n = 45	No significant difference in clinical outcomes between the favipiravir + IFN-β & HCQ in adults hospitalized with moderate to severe COVID-19 pneumonia.
6	Monk PD et al. (2020) [23] Randomized, Double blind control Study	101	28 days	Administration of nebulized Interferon beta-1a (SNG001) to 48/101 and nebulized placebo to 50/101 daily for 14 days with an objective assessment of improvement in clinical state as the primary outcome.	Participants in the test group had greater chances of recovery and more speedy recovery as compared with participants in the control group.
7	Emin Gemcioglu et al. 2020 [27] Case Report	1	7 days	Pt on IFN-β for 2 years for MS. Hydroxychloroquine, azithromycin and enoxaparin sodium treatment were initiated as an addition to interferon therapy; Therapy maintained for 5 days	Not only length of hospital stay was shorter but also symptoms remained markedly faint
8	Nakhlband A et al. (2021) [28] Systematic review and Meta-analysis	314	Not applicable	Standard care (hydroxychloroquine and lopinavir/ritonavir) *vs.* intervention care protocol (standard care + IFN-β) The author mentions that in most of their studies: IFN-β was given SC at 44 microgram/ml × 3 times/week for 2 consecutive weeks.	According to meta-analysis, a significant difference was found between intervention and control group with overall discharge rate (RR = 3.05; 95% CI: 1.09 - 5.01). No significant heterogeneity ($P = 0.46$). Only one RCT had reported 2% mild to moderate adverse event was recorded.

IFN, interferon; s/c, subcutaneos; OR, odds ratio; CI, confidence interval; HCQ, hydroxychloroquine; BID, twice a day; P.O, taken by mouth; QID, four times a day; ICU, intensive care unit; MS, multiple sclerosis; RR, relative risk; RCT, randomized clinical trial.

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3. Risk-of-bias assessment

To assess each study's risk of bias, these critical criteria were utilized: selection bias, allocation concealment, performance bias, detection bias, publication bias, exclusion bias, and other sources of bias. The Cochrane Reviews were used to pass the following judgments: high risk, low risk, and unclear due to lack of information or any type of uncertainty [19]. Studies found to have poor methodological quality or have a high risk of bias were excluded. Disagreements will be resolved when discussed with other authors.

4. Risk of bias assessment and judgements

Two open-label Randomized trials, where patients, caretakers, and investigators were unblinded, have a high risk of performance bias and an increased risk for allocation concealment (selection bias) [20, 21]. One prospective non-controlled trial [22] had attrition bias since the study only lasted 14 days. This study [22] also had an unclear selection, performance, and detection bias.

Low risk of bias was detected in two studies [16, 23]. Unclear bias was detected in four studies [24-27] because these studies explained the mechanism, pathogenesis, or the effect on the virus or in vitro experiment without any human trials.

Detection bias was observed in some studies where the period between the intervention and the outcome was different for the cases vs. the patients' in the controlled group. Exclusion Bias was observed in most of the studies. For example, patients with certain underlying conditions were excluded, pregnant and lactating mothers were also excluded; all excluded minors below 18 years old. Another source of bias was noted in one study [28]. Between 54 to 75 percent of the participants were male patients with a mean age above 55 years, showing low diversity both in age groups and sex. Performance bias is uncertain since it is likely that the patients in the study were blinded but it was not reported or described. The risk of bias for said study was low otherwise [28]. Publication bias was not noted in any of the studies of treatments for COVID-19. Since COVID-19 is a relatively new disease, there is insufficient information to determine other forms of biases. There is potential for both unconscious and funding bias [29, 30].

RESULTS

Effat Davoudi-Monfared and Hamid Rahmani *et al.* [16] conducted two open-label, randomized clinical trials to assess the efficacy and safety of IFN-β 1a in the treatment of adults (aged ≥18 years) patients diagnosed with COVID-19. Patients were admitted to Imam Khomeini Hospital Complex, the main central hospital in Tehran, Iran's capital.

The first was done from February 29 to April 3, 2020, and the other from April 20 to May 20, 2020. The primary outcome of the study was time to reach a clinical response. Secondary outcomes were duration of mechanical ventilation, duration of hospital stay, length of intensive care unit (ICU) stay, 28-day mortality, effect of early or late (before or after 10 days of the onset of symptoms) administration of IFN on mortality, adverse effects, and complications during the hospitalization.

Considering dropouts, Study 1 had 81 patients (42 in the IFN and 39 in the control group), and Study 2 had 66 patients (33 in the IFN and 33 in the control groups) who completed the

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treatment for further analysis. Dropouts in the first study: 4 in the IFN group (2 died before the second dose of IFN, 2 died before the third dose of IFN), 7 in the control group (entered another trial). Dropouts in the second study: 4 in the IFN group (2 discontinued IFN after the second dose, 2 discontinued after the third dose), 3 in the control group (entered another trial).

National protocol medications (hydroxychloroquine (400 mg twice a day [BID] on the first day and then 200 mg BID) plus lopinavir-ritonavir (400 and 100 mg, respectively, BID) or atazanavir ritonavir (300 and 100 mg, respectively, daily) for 7 to 10 days. Although IFN did not change the time to reach a clinical response, added to the national protocol, it significantly increased the discharge rate on day 14 and decreased 28-day mortality. Improved survival rate was significant in the first study with 81 participants, especially when patients received IFN-β-1a in the early phase of the disease. In Study 2 with 33 participants, there was no significant difference between the groups; and they recommend that further trials be done with enough sample size to estimate the survival benefits of IFN-β-1 accurately. Adverse effects of IFN-β-1a were injection-related, neuropsychiatric problems, and hypersensitivity reactions that all were tolerable and resolved during the follow-up period.

Dastan *et al.* [22] did a prospective non-controlled trial of subcutaneous administration of IFN-β-1a for COVID-19. Of the 64 eligible patients, 20 were included and completed the study. The mean age of the patients was 58.55. The youngest patient was 37 years old, and the oldest patient was 86 years old. The male-to-female ratio in the study was 4:1. Time of symptom onset until hospitalization was 6.5 ± 2.8 days. The results revealed that 15 patients had a fever, 16 had a cough, and 17 had dyspnea at admission. Malaise was noted in all patients. Fever resolved in all patients after 8 days. Although other symptoms decreased gradually, however cough, dyspnea, myalgia and malaise persisted. Most patients received high flow oxygen with nasal cannula during hospitalization. Three patients received noninvasive mechanical ventilation for low oxygen saturation. These patients were weaned from the noninvasive mechanical ventilation after 5 to 10 days. The mean time of hospitalization was 16.8 days. There were no deaths or significant adverse drug reactions in the 14 days. Laboratory parameters were measured at admission and on days 7 and 14. The mean SD of white blood cell (WBC) was 5.10 ± 1.41 at admission, which increased to 8.32 ± 5.55 on day 7. The mean ± SD of lymphocyte count was 1,126.86 ± 311.06 on day 1; 2,103.32 ± on day 7; and 1303.44 ± 463.22 on day 14. No abnormality was noted in hemoglobin, platelets, urea, creatinine, aspartate transaminase, alanine transaminase, and alkaline phosphatase levels. The virological clearance study showed that all patients had positive RT-PCR samples on admission time. On day 10, all patients had negative RT-PCR samples except two patients. Lung CT and X-ray were performed on admission and day 14. CT images revealed ground-glass opacity in 16 patients, and X-ray images revealed bilateral infiltrates in 14 patients, and recovery occurred after 14 days.

Ngai Hung *et al.* [20] conducted a randomized trial in patients admitted to the hospital with COVID-19 using a triple combination treatment (IFN-β-1b, lopinavir-ritonavir, and ribavirin). This multicenter randomized open-label phase 2 trial screened 144 patients and recruited 127 patients for the study, who constituted 80% of COVID-19 cases from February 10 to March 24, 86 patients were randomly assigned to the combination group, and 41 were assigned to the control group. 9 patients did not fulfill the inclusion criteria, and 8 patients declined the treatment regimen. One patient in the control group required discontinuation of lopinavir-ritonavir because of elevated alanine transferase after one treatment week. The median age was 52 years, 68 men *vs*. 59 women. The age, sex, and baseline demographics in each group

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were similar. Within the combination group, 52 patients admitted to the hospital less than 7 days from symptom onset received the lopinavir-ritonavir, ribavirin, IFN-β-1b regimen, and 34 patients admitted 7 days or more after symptom onset received the lopinavir-ritonavir only regimen. The median number of doses of IFN-β-1b received was two. Median time from symptom onset to start of treatment was 5 days for the combination group and 4 days for the control group. Fever and unproductive cough were the most common presenting signs and symptoms. Disease severity on presentation was mild, based on NEWS2 and SOFA score. The combination group had a significantly shorter median time (7 days) than the control group (12 days) for the primary endpoint of time from the start of study treatment to negative nasopharyngeal swab. The combination group had a better clinical and virological response reflected in the shorter median hospital stay (9 days *vs.* 14 days: Hazard Ratio 2.72 [1.2 - 6.13], $P = 0.016$). The baseline viral loads for all specimens were similar between the combination group and control group. The nasopharyngeal swab viral load was significantly lower in the combination group than in the control group from day 1 to day 7 after treatment. Post hoc subgroup comparison of the 76 patients who started treatment less than 7 days after onset of symptoms showed better clinical and virological outcomes in the combination group (52 patients, receiving lopinavir-ritonavir and IFN-β-1b) than in the control group (24 patients) across all measured variables except stool samples. However, no significant differences between the treatment groups were measured in these outcomes in the 51 patients treated 7 days or after symptom onset (34 in the combination group and 17 in the control group). 17 of 127 patients required oxygen treatment, and 6 patients got admitted to the intensive care unit, of whom 5 required noninvasive ventilator support and one patient with a past medical history of coronary artery disease (CAD) required intubation and ventilator support.

The serum cytokine profile was analyzed in the first 84 recruited patients. The IL-6 concentration in the combination group was significantly lower than in the control group on days 2,6, and 8. Multivariable analysis showed that the combination group and having a nonpathological baseline chest-X-ray were independently associated with day 7 negative nasopharyngeal swab viral load. It was reported that 41 out of 86 patients presented adverse events in the combination group and only 20 out of 41 in the control group. From these adverse events, the most common were diarrhea, fever, nausea and elevated alanine aminotransferase (ALT). 4 patients reported sinus bradycardia. These side effects resolved within 3 days after drug initiation. There was no difference between the incidence of any adverse events or the duration of nausea or diarrhea between the treatment groups. No patients died during the study.

Khamis *et al.* [21] performed a Randomized Control Trial in Royal hospital, Muscat, Oman. This was to evaluate the effectiveness of Favipiravir with inhaled IFN-β-1b (given in n = 44) compared to hydroxychloroquine (given in n = 45) in hospitalized COVID-19 patients with moderate to severe pneumonia. Their study was extended for 6 weeks from June 22, 2020 - August 13, 2020. The authors found no difference in both the groups in terms of the inflammatory markers, improvement in oxygenation, Transfer to ICU, or time to recovery. The *P*-value for all the parameters was >0.5. All the participants were closely monitored for any changes in their hepatic parameters, and the dose age of the drugs was modulated accordingly. They did not report any significant side effects such as hyperuricemia, elevated liver enzymes, or QTc prolongation due to the use of favipiravir. However, they recommend further studies to be done until then to use favipiravir cautiously outside of clinical trial settings. The authors also note that there is not much study about the pharmacokinetics or pharmacodynamics of intranasal IFN-β-1b, which poses a limitation on this study where this was the chosen route of administration.

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Monk *et al.* [23] conducted a Randomized, double-blinded, control trial lasting 28 days in several sites in the UK. Aimed at assessing the safety and efficacy of nebulized IFN-β-1a (SNG001) for treatment of COVID-19, 50 individuals were assigned to the test group and 51 to the control group. The participant pool ranged from age ≥18 years, and baseline supplementation of oxygen was required in the test (37/48) and control (29/50) groups.

Participants in the test group received daily, nebulized SNG001, while participants in the control group were administered placebo for 14 days. Monitoring adverse effects was conducted simultaneously with intervention up to 14 days after the intervention, thus totaling 28 days. Participants in the test group had greater chances of recovery as determined by the WHO's Ordinal scale for clinical improvement (OSCI) [odds ratio 2.32 [95% confidence interval [CI] 1.07 - 5.04]; $P = 0.033$], and an increased chance of attaining an OSCI score of 1.

Adverse effects related to COVID-19 were reported less in the test group (3 cases of respiratory failure and pneumonia each) than the control group (6 cases of respiratory failure and 3 cases of pneumonia). Headache was the most adverse effect on the overall reported in 15% of the test group (7) and 10% of the control group (5). SNG001 was well tolerated, and no case of mortality was recorded in the test group; there were 3 cases of mortality in the control group. As findings from this trial suggest clinical benefits from SNG001 use, the authors suggested further clinical trials for further assessments.

Emin Gemcioglu *et al.* [27] published a case report of a 31/M with multiple sclerosis who showed shortened hospital stay and no complications. The patient has been treated with type 1 IFN-β for 2 years before being exposed and testing positive for COVID-19. The paper, which was published in a journal for Multiple Sclerosis did not indicate how the patient took IFN-β or the dose and timing he was taking. IFN-β injectable is a mainstay medication for multiple sclerosis and the patient has been taking it for 2 years outside of his COVID-19 diagnosis. One week after exposure, he went to the ER and was then admitted to the hospital with a case of COVID-19 pneumonia. Besides stable multiple sclerosis, the patient's only other comorbidity is seasonal allergies. The patient complained of dry cough and shortness of breath complaints. He had no fever. The physical examination, respiratory sounds were nonpathological. During his 7-day hospital stay, respiratory rate and oxygen saturation were normal. WBC, HGB, PLT, C-reactive protein level, liver function tests, kidney function tests, D-dimer level were normal. Hydroxychloroquine, azithromycin, and enoxaparin sodium treatment were initiated as an addition to his interferon therapy; Therapy was maintained for 5 days, and the patient was discharged on the 7 days of admission. The authors write that this patient's flat symptoms and fast recovery from COVID-19 pneumonia point to seeing IFN-β as a possible treatment for COVID-19.

Nakhlband A et al. [28] performed a systematic review and meta analysis of 314 patients, to compare the standard care (hydroxychloroquine and lopinavir/ritonavir) for severe manifestations of COVID-19 patients with the intervention care protocol (standard care +IFN-beta). After a systematic search, the authors included 3 studies for a meta-analysis, and 5 for a systematic review, in total 314 patients. In their meta-analysis they found a significant difference between intervention and control groups, with overall discharge rate (Relative Risk = 3.05; 95% CI: 1.09 - 5.01). They also recorded that mean days of hospitalization among both the study groups ranged from 6.75 to 16.8 days. There was also no significant heterogeneity ($P = 0.46$).

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DISCUSSION

1. Main findings concerning the efficacy of IFN-β

In this systematic review, the main findings concerning IFN-β efficacy indicate that patients with SARS-CoV-2 confirmed infection who received an early administration of IFN-β have a significantly reduced length of hospitalization, mortality, ICU admission, and intubation rate. The patients also experienced milder symptoms and had a greater chance of recovery on day 14. Clinical improvement could be seen in imaging studies of all the patients after this period. Additionally, Dastan *et al.* [22] and Ngai Hung *et al.* [20], in their various studies of 1 month and 6 weeks respectively using a combination of IFN-β with conventional therapy in a total of 188 COVID-19 patients, did not report any death. However, findings from Dastan *et al.* [22] propped up the use of IFN-β 1 A in combination with hydroxychloroquine and lopinavir/ritonavir to manage COVID-19 infection. Moreover, based on the small samples of the available studies, further randomized clinical trials with greater sample size are needed to accurately estimate the survival benefit of IFN β-1b.

Using IFN-β may not be entirely justified from a health-economic perspective in preventive treatment for COVID-19. However, it seems to be a good cost-effective strategy for the management of individuals with a SARS-CoV-2 diagnosis due to the potential improvement of their survival rate, while investigating curative new antiviral drugs for COVID-19 infection [32].

2. Overall completeness and applicability of evidence

Being dealing with a new disease, one of the significant challenges we face is a lack of knowledge about the efficacy and safety of a medication. So far, there is no simple treatment that has shown full effectiveness, and combinations of therapies seem to be more beneficial in some cases of COVID-19.

Mantlo *et al.* [25] demonstrated that SARS-CoV-2 replication is inhibited by IFN-α and IFN-β, in vitro, at clinically achievable concentrations in patients [25]. This certainty opens a door for interferon use either alone or in combination for the treatment of COVID 19.

In a study by Monk *et al.* [23] at nine sites in the UK, inhaled nebulized IFN-β-1a (SNG001) was well tolerated in patients admitted to the hospital with COVID-19, with a range of clinical outcomes that showed improvement in COVID-19 patients' health [23]. This warrants that more extensive studies be done globally.

However, pharmacologically the combination of therapies seems to be the way to achieve better results. The use of antiviral drugs that act at different levels of the virus life cycle in conjunction with the activation of genes stimulated by interferon has been shown to improve patients' clinical outcomes. Various studies have been published and help corroborate the veracity of this hypothesis [16, 20,22, 24].

Effat Davoudi-Monfared *et al.* [16] present a randomized clinical trial about efficacy and safety of IFN-β in patients with severe COVID-19. It was observed that adding IFN-β to the national protocol medications significantly increased the discharge rate on day 14 and decreased 28-day mortality, although IFN did not change time to reach the clinical response. In another randomized clinical trial conducted by Rahmani *et al.* [24], the efficacy of IFN-β -b in addition to their national protocol regimen was also evaluated. A significant clinical improvement was seen in the IFN-β-1b group, with a remarkable mechanical ventilation reduction and ICU admission.

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Hung *et al.* [20] carried out a randomized, phase 2 trial that examined the effect of a triple combination regimen of IFN-β-1b, lopinavir plus ritonavir compared with lopinavir plus ritonavir alone. The efficacy was safe and higher in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.

A non-controlled prospective trial evaluated the therapeutic efficacy and safety of IFN-β-1a in patients with COVID-19 [22]. The results revealed the efficacy of IFN-β-1a in combination with hydroxychloroquine, and lopinavir/ritonavir in reducing the disease symptoms with a dramatic response to this combination treatment. No significant adverse drug reactions or mortality was noted in these studies.

In a systematic review and meta-analysis to evaluate the therapeutic effects of IFN-β in severe COVID-19 patients done by Nakhlband *et al.* [28], was found that IFN-β is an innovative therapeutic option against COVID-19, and the combination of IFN-β with antiviral drugs demonstrated more promising results in treating COVID-19. On the other hand, we cannot fail to mention that a randomized controlled open-label trial on antiviral use combined with inhaled IFN-β-1b, conducted by Khamis *et al.* [21], showed no differences in inflammatory markers or clinical outcomes in COVID-19 patients with moderate to severe pneumonia.

3. Did this review generate a novel perspective?

Our review implies that IFN-β may help COVID-19 patients recover faster without any limitations of severe adverse effects. Moreover, different modes of administration can affect its efficacy. The non-peer-reviewed preprint of the WHO SOLIDARITY trial reported that Subcutaneous IFN-β 1a was not effective in treating COVID-19 patients because subcutaneous delivery does not directly target the lungs as inhalation does. The inhaled form of interferon B has additional benefits of managing COVID-19 infection when it occurs with concurrent respiratory infections by another virus, such as influenza or respiratory syncytial virus (RSV) that may be encountered during winter.

4. Limitations of studies included in the review

Due to the novelty of COVID-19, several notable limitations were observed in the selected studies. The constraints of the methodology and research design influenced the interpretation of the results of the studies. Most of the selected human trial studies were conducted abroad in Iran, China, Oman, Taiwan, and the UK, with one vero cell study in the US [20]. Thus, the results cannot be used as a representation or a guideline in treating the virus worldwide, where different standards of care exist. Some reported limitations included a small sample size, lack of control groups, and absence of follow-up. Some of the studies reported a limitation in resources. Thus the outcome and effect of interferon-beta on the virus could not be appropriately measured. Another type of limitation was the lack of academic resources of prior research done on COVID-19. An increase in sample sizes and more extensive trials could help determine whether patients undergoing treatment with IFN-β would have higher survival rates in future research.

In conclusion, this research shows encouraging data on IFN-β 1b effectiveness against the novel COVID-19 infection. When added to the current standard of care, IFN-β has been shown to decrease the overall hospitalization stay and decrease the severity of COVID-19 respiratory symptoms. Some studies have reduced ICU stay, enhanced the survival rate, and decreased invasive mechanical ventilation needs in severe cases compared to control. Adverse effects in COVID-19 patients receiving IFN-β included neuropsychiatric symptoms, diarrhea,

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fever, nausea, and mild ALT elevations. One case of hypersensitivity was recorded. The above studies show the promising outcome of adding IFN-β for the treatment of hospitalized COVID-19 patients. However, further randomized clinical trials with a large sample size are needed to precisely assess the survival benefit of IFN-β-1b.

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