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REVIEW ARTICLE

Interferon-beta offers promising avenues to COVID-19 treatment: a systematic review and meta-analysis of clinical trial studies

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Abstract

Severe acute respiratory syndrome coronavirus 2 principally weakens the hosts' innate immune system by impairing the interferon function and production. Type I interferons (IFNs) especially IFN-β are best known for their antiviral activities. IFNs accompanied by the standard care protocols have opened up unique opportunities for treating the coronavirus disease 2019 (COVID-19). The databases including PubMed, SCOPUS, EMBASE, and Google Scholar were searched up to October 30, 2020. The primary and secondary outcomes were considered discharge and mortality, respectively. The abovementioned outcomes of standard care protocol were compared with the standard care plus IFN-β in the confirmed COVID-19 patients. Out of 356 records identified, 12 randomized clinical trial studies were selected for full-text screening. Finally, 5 papers were included in the systematic review and 3 papers in the meta-analysis. The average mortality rate was reported as 6.195% and 18.02% in intervention and control groups, respectively. Likewise, the median days of hospitalization were lower in the intervention group (9 days) than the control group (12.25 days). According to meta-analysis, IFN-β was found to increase the overall discharge rate (RR = 3.05; 95% CI: 1.09–5.01). Our findings revealed that early administration of IFN-β in combination with antiviral drugs is a promising therapeutic strategy against COVID-19.

Keywords COVID-19 · Interferon-β · Discharge · Review

Introduction

Coronavirus disease 2019 (COVID-19) has become a global public health emergency of international concern since it has led to the greatest pandemic of the century (Durrheim et al. 2020; Azizi and Davtalab-Esmaeili 2020). Despite many efforts to find a promising therapy worldwide, no approved efficient treatment has been introduced so far. Some evidence reveals that COVID-19 severity is correlated with interferon-beta (IFN-β) levels and impairment (Rameshrad et al. 2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus causing COVID-19; this virus ceases host IFN production via proficient mechanisms. Moreover, comorbidities may impress IFN production adversely and impair inflammatory responses (Hadjadj et al. 2020; Rameshrad et al. 2015).

On the other hand, it is well-documented that IFN is an antiviral agent with protease inhibition capacity (Sujaritha et al. 2020). In vitro studies in VeroE6 cells have shown inhibitory effects of type I interferon (IFN I) against replication of SARS-CoV-2, as well as in terms of viral antigen expression, viral load reduction, and plaque reduction assays (Lokugamage et al. 2020). Moreover, the potential of interferon-beta-1b in attenuation of virus-induced lung fibrosis in a mouse model might be beneficial for COVID-19 patients with acute respiratory distress syndrome (ARDS) (Hung et al. 2020).

In brief, encountering a virus, type I IFNs (among them IFN-β) induced promptly and arranged a corresponding

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antiviral action via interferon-stimulated genes (ISGs); but disastrously it was observed that ISGs are down-regulated extremely in COVID-19 patients.

To date, IFN-β is among the promising therapeutic options for COVID-19 owing to its antiviral and anti-inflammatory potentials. Some clinical trials have investigated potential of IFN-β in suppressing COVID-19. In addition, the administration of IFN-β was considered a promising approach in managing even severe cases of COVID-19.

In the event of such an emergency, summarizing and analyzing the existing data may provide new insights in interpreting the outcomes as well as demonstrating promising therapeutic options. Therefore, we conducted a systematic review to assess outcomes of IFN-β treatment in COVID-19 patients.

Materials and methods

In this study, we performed a systematic review and meta-analysis to evaluate the therapeutic effects of IFN-β in severe COVID-19 patients. There were two inclusion criteria for article selection: (1) hospitalized patients with COVID-19 receiving IFN-β and (2) be either a randomized controlled trial (RCT) or a cohort study.

Outcomes

Discharge from the hospital (mean days of hospitalization) and mortality rate were considered the primary and secondary outcomes, respectively.

The time (days) from onset of symptoms to treatment initiation (with interferon) was evaluated in all studies for identifying the best times of IFN administration after onset of symptoms. Symptoms including fever, white blood cells (WBCs) and lymphocyte count, and stage of disease were considered and evaluated in all included studies.

Comparison

The standard care (hydroxychloroquine and lopinavir/ritonavir) for severe COVID-19 patients was compared with the intervention care protocol (standard care + IFN-β).

Search strategy

Databases including PubMed, SCOPUS, EMBASE, and Google Scholar were searched up to October 30, 2020. The reference lists of all identified records were screened to find out more relevant studies. There were no language restrictions. The search keywords included "2019-CoV," "2019 novel coronavirus," "COVID-19," "coronavirus disease 2019," "beta Interferon," and "alpha Interferon."

Selection of studies

The identified records were screened by two authors independently, and the relevant information were extracted. Discrepancies and disputes were resolved by consensus and participation of one more author.

Data extraction

We included five records in the review. All necessary data including sample size, therapeutic effects of interferon, onset of signs and symptoms, days of discharge from hospital, mortality rate, outcomes, and type of intervention were collected in a predesigned EXCELL form by brief explanations.

Statistical analysis

STATA software (version 13.0) was used for data analysis. Discharge from the hospital was considered the outcome variable. We used hazard ratio (HR) for estimating the point estimate with 95% confidence interval (CI). We applied the meta-analysis using the Mantel-Haenszel method for the dichotomous variables and the random-effects model for the pooling of data.

Results

Through searching 4 databases, we identified 356 records. The retrieved records were evaluated for duplication, and the titles and abstracts were reviewed according to the inclusion criteria. Out of 356 records, 12 RCTs and cohort studies were selected for full-text screening. Finally, 5 records were included in the systematic review, and 3 articles were included in the meta-analysis.

The total participants were 314 patients. The PRISMA flow diagram shows the included studies (Fig. 1). After full-text screening, 7 records were excluded (alpha Interferon = 5, study design (protocol) = 1, retrospective study =1).

Baseline characters

Table 1 shows the details of the included studies. Males were the major participants in all the studies. The proportion of male patients ranged from 54.0% to 75.0% (median 60.0%). The mean age of participants in most studies was higher than 55 years.

Clinical symptoms

All articles had investigated hospitalized patients with mild to severe COVID-19. In the intervention group, the proportion of intensive care unit (ICU) admissions was lower than control

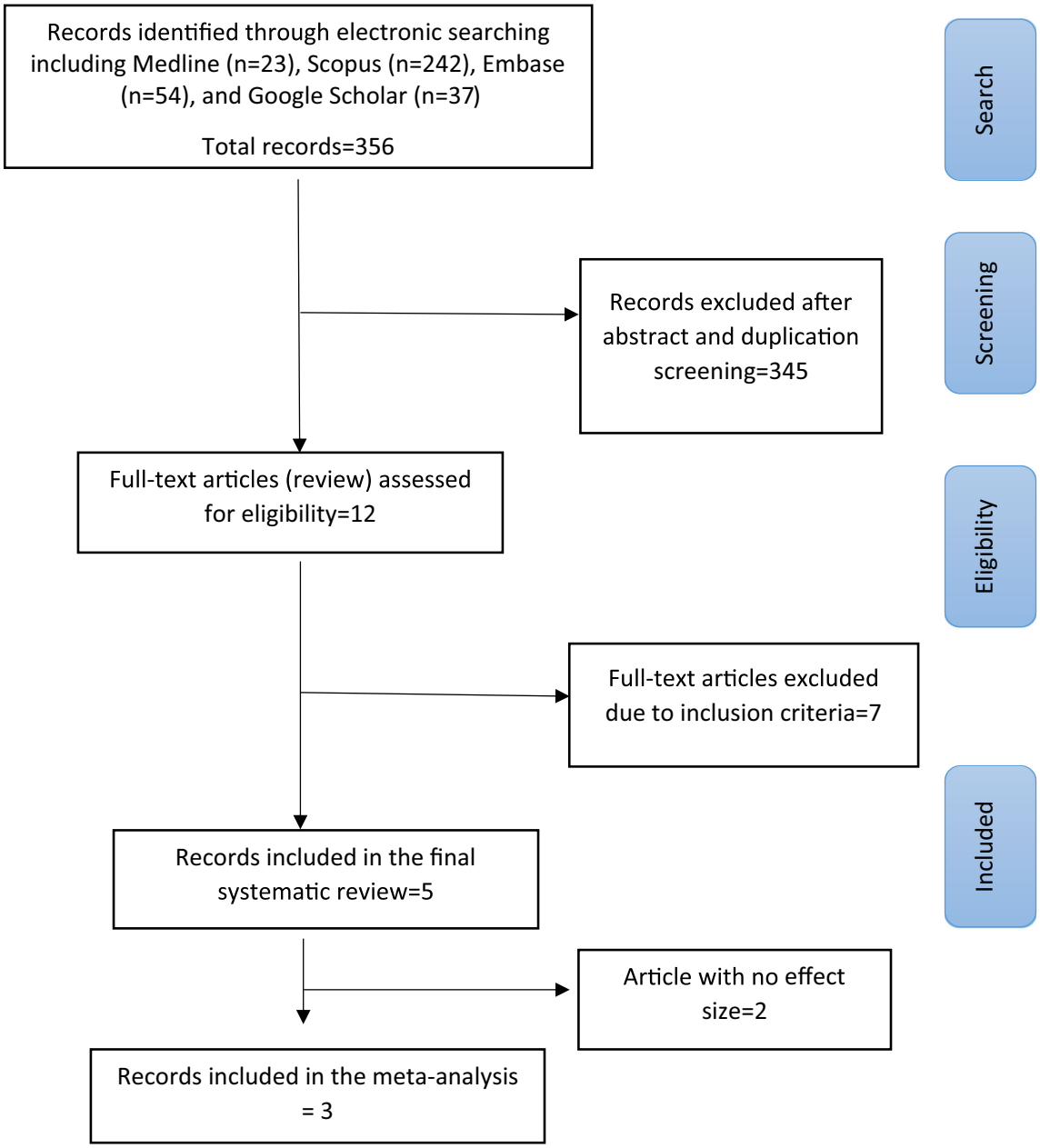


Fig. 1 Search flow diagram

groups. In a study by Monfared et al. from Iran, the proportion of ICU admission was reported 45.23% and 58.97% in intervention and control groups, respectively (Davoudi-Monfared et al. 2020). Besides, same result was reported by Rahmani et al. in a RCT study for ICU admission proportion (42.42% vs. 66.66%) (Rahmani et al. 2020). Likewise, in an RCT carried out in Hon Kong, Fan-Ngai Hung et al. reported that the times (days) of early warning scores of 0 (according to a national early warning score 2) were 4.0 and 8.0 days among intervention and control groups, respectively. They demonstrated that there is a significant relationship between INF-β intervention and decrease in ICU admission and time of early warning score of zero. Moreover the treatment with the antiviral combination decreased IL-6 levels significantly, whereas it did not show any significant impact on TNF α and IL-10 concentrations (Hung et al. 2020) (Table 2).

All patients in all the included studies showed fever at admission. In the intervention group, the fever of the majority of participants was resolved at the end of the study period. In most of the studies, WBC and lymphocyte counts were increased in the intervention group. A study by Dastan et al. demonstrated that the fever of all patients was resolved during the first seven days. Likewise, fever was resolved in 81% and 78% of patients in the intervention and control groups, respectively. Moreover, comparing the lung CT and chest X-ray at admission and on day 14 showed ground glass opacity in 16

Table 1 Included clinical trial studies and baseline characteristics among COVID-19 patients treated by IFN-β

Author	Country	Mean age ± SD	Sex (male %)	Type of study	N of patients	Study groups		Treatment onset from symptom onset	Stage of disease	ICU admission
						Intervention	control			Intervention/ control
Rahmani et al. (2020)	Iran	60 (47–73)	59%	Open-label randomized clinical trial	66	IFN β-1b	Standard care (lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine for 7–10 days)	Not reported	Severe	42.42% vs. 66.66%
Dastan et al. (2020)	Iran	58.55 ± 13.43	75%	Prospective non-controlled trial	20	IFN-β-1a + hydroxychloroquine (200 mg P.O. BID) and lopinavir/ritonavir (200/50 mg P.O.; two tablets QID) for 5 days	Non-controlled trial	6.5 ± 2.8 days	Severe	Non-controlled
Monfared, et al. (2020)	Iran	IFN: 56.0 ± 16 Control: 59.5 ± 14	54.3%	Open-label randomized clinical trial	81 (42 in the IFN and 39 in the control group)	IFN-β-1a + Hydroxychloroquine (400 mg BD in first day and then 200 mg BD) plus lopinavir/ritonavir 155 (400 /100 mg BD) or atazanavir/ritonavir (300/100 mg daily) for 7-10 days+ 35.7% of patients received intravenous immunoglobulin (IVIG)+ 61.9% of patients received corticosteroids	Hydroxychloroquine (400 mg BD in first day and then 200 mg BD) plus lopinavir/ritonavir (400/100 mg BD) or atazanavir/ritonavir (300/100 mg daily) for 7–10 days. + 25.6% of patients received intravenous immunoglobulin(IVIG)+ 43.6% of patients received corticosteroids	10 days	Severe	45.23% vs 58.97%
Payandemehr, et al. (2020)	Iran	55.5	60%	Investigator initiated, open-label, single-arm clinical trial	20	Not reported	hydroxychloroquine (200 mg twice daily), lopinavir/ritonavir (200/50mg four times daily), oseltamivir (75 mg, twice daily) and ribavirin (1200 mg twice daily)	<7 days	Moderate to severe symptoms	10%
Fan-Ngai Hung et al. (2020)	Hong Kong	52	54%	Multileft RCT	127(2:1)	IFN-β-1b + lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h	Lopinavir 400 mg and ritonavir 100 mg every 12 h	5 days	Hospitalized (severe)	Time to early warning score of 0, days 4.0/8.0 (p=0.001)

Table 2 Outcome and clinical measures among COVID-19 patients treated by IFN-β

Author	IFN-β dose	Interferon type	Interferon administration	Resolved fever	Measured CBC		Hospitalization or discharge (intervention/control)	Mortality	Serious adverse effects
					WBC count	Lymphocyte count			
Rahmani et al. (2020)	250 mcg subcutaneously every other day for two consecutive weeks	IFN β-1b	Subcutaneous	54.5% vs. 63.6%	5400 (4025–8250) vs. 5900 (4050–7650)	924 (520–1400) vs. 869 (670-1000)	Discharge (78.79% vs 54.55%)	6.06% vs. 18.18%	No
Dastan et al. (2020)	44 μg subcutaneously every other day up to 10 days. (equivalent to 12 million international units)	IFN-β-1a	Subcutaneous	Resolved in all patients during first 7 days	Increased	Increased	Mean ±SD: 16.8 ± 3.4 days	0% in 14 days	No
Monfared et al. (2020)	44 micrograms/ml (12 million IU/ml) of interferon β-1a three times weekly for two consecutive weeks	IFN-β-1a	Subcutaneous		8345±4632/7686 ±4033	Not reported	14.80 ± 8.45/12.25 ± 7.48	19%/43.6% in 28 days	Not different between the groups
Payandemehr et al. (2020)	(44 μg every day until discharge or until 5 days of admission	IFN-β-1a	Subcutaneous	The most common symptom of the patients at onset of disease was fever. None of the patients had fever even in follow-up	5.9×103	20.7%	6.75 (±9.2) days	One of them died after 45 days of hospitalization	No adverse effects reported
Fan-Ngai Hung et al. (2020)	three doses of 8 million international units of interferon-beta-1b on alternate days	beta-1	Subcutaneous	81% vs 78%	4.9 vs 5.4 × 10^9 per L	1.0 vs 1.3 × 10^9 per L	9.0 vs 14.5 days	0.0% vs 0.0%	0.0% vs 2%

patients and bilateral infiltration in 14 patients which demonstrated occurrence of recovery at 14 days (Dastan et al. 2020).

The time of the onset of symptoms from treatment initiation ranged from 5 to 10 days. The shortest time of IFN administration after symptoms initiation was reported by Hong Kong. This investigation reported no mortality at the end of the study. The longest time from the onset of symptoms to interferon administration was reported by Monfared et al. in Iran; at the end of this study, death rates were reported 19% and 43.6% in intervention and control groups, respectively (Davoudi-Monfared et al. 2020).

Intervention (IFN-β dose)

In most studies, 44 micrograms/ml (12 million IU/ml) of INF-β was administered three times a week for two consecutive weeks or until discharge. In all studies, INF-β was administrated subcutaneously. Moreover, most studies reported no serious adverse effects of interferon therapy among the intervention groups. Only in a multicenter RCT carried out in Hong Kong, the researchers reported 2% adverse effects of interferon therapy; however, they were mostly mild and self-limiting (Hung et al. 2020).

Outcomes

We found that outcome measures (discharge and mortality rate) were decreased in all studies in the intervention group. The mean days of hospitalization among both study groups ranged from 6.75 to 16.8 days; however, the median days of hospitalization in intervention groups (9 days) were lower than control groups (12.25 days).

Regarding the mortality rate, Rahmani et al. reported that mortality and discharge were 6.06% vs 18.18% and 78.79% vs 54.55% in the IFN vs control groups, respectively (Rahmani et al. 2020). Another study (Dastan et al.) did not have any control group for comparing the results. Likewise, in one study, no mortality occurred in intervention and control groups during the study.

However, the average mortality rate in the INF-β group and the standard group was 6.195% and 18.02%, respectively.

In the multicenter RCT by Fan-Ngai Hung et al. in Hong Kong, the mean days of hospitalization in the intervention and control groups were 9.0 and 14.5 days, respectively. Furthermore, they reported no death in the intervention and control groups at the end of the study (Hung et al. 2020). In the RCT from Iran, the mortality rate of intervention and control groups was reported as 19% and 43.6% during 28 days of the study period. In contrast, this study reported that the duration of hospitalization in the intervention group was more than the control group (14.80 ± 8.45 vs 12.25 ± 7.48) (Davoudi-Monfared et al. 2020). In another open-label single-arm clinical trial, only one death was reported after 45 days of hospitalization (Payandemehr et al. 2020). In another non-controlled study, fever resolved in all patients during the first 7 days (Dastan et al. 2020).

Meta-analysis

Out of four included studies, three studies had effect size (HR and OR) for discharge probability to compare the therapeutic effects of INF-β among study groups (standard care group and INF-β group). Only one study reported the measure of effects for mortality rate. Therefore, we conducted a meta-analysis to evaluate the prevalence rate of discharged patients among three studies. In all studies, the discharge rates were significantly associated with INF-β therapy. According to meta-analysis, a significant difference was found between intervention and control groups with the overall discharge rate (RR = 3.05; 95% CI, (1.09–5.01). There was no significant heterogeneity (P=0.46) (Fig. 2).

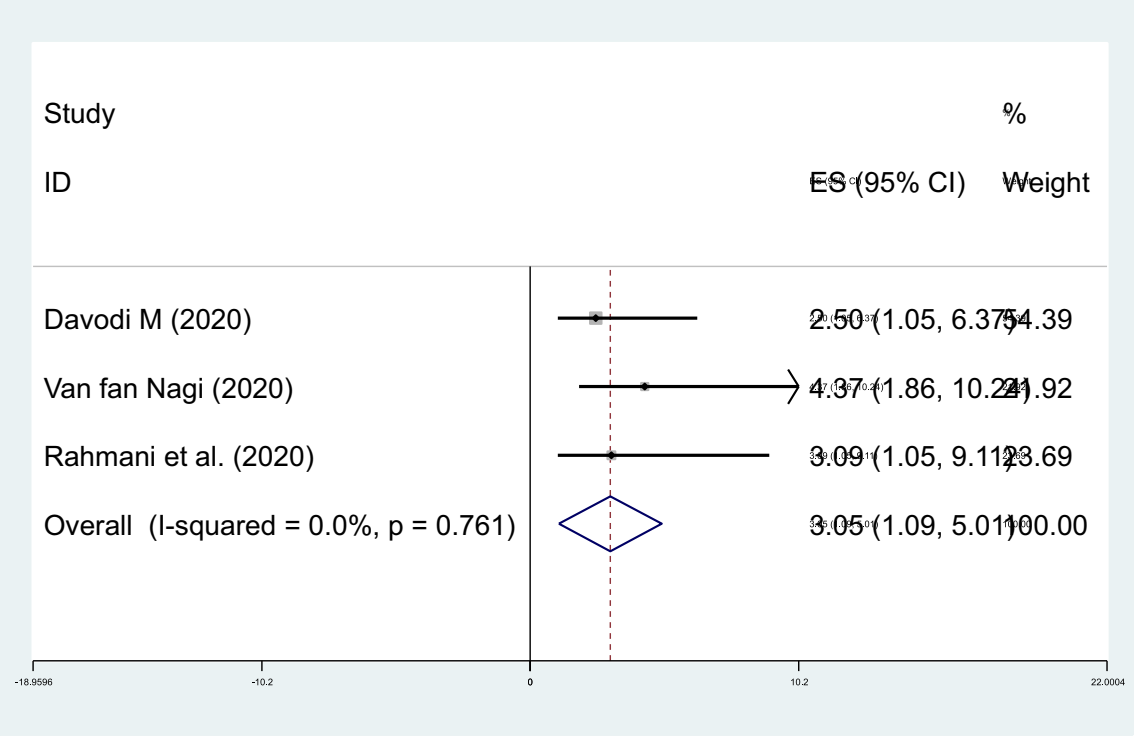
Discussion

Crucial searches for practical prophylactic and therapeutic interventions are promptly developing worldwide with the end of combating against COVID-19. Of them, type I interferon, mainly IFN-β, has been potentially employed as one of the primary therapeutic options. In this systematic review and meta-analysis, we showed that INF-β in combination with antiviral drugs (lopinavir/ritonavir) efficiently suppresses the SARS-CoV-2 in terms of decreasing the duration of hospitalization and mortality rate.

Currently, IFNs are the favored drugs to treat virus infections such as chronic hepatitis B and C, cancer, and multiple sclerosis (MS). Type I interferon has the key roles in the immediate antiviral response and innate immune response, while it has been well proved that production and activity of IFNs are impaired in severe COVID-19 cases. IFNs overcome viruses via several mechanisms such as linking the innate and adaptive immune responses. It has been well established that SARS-CoV-2 open reading frame (ORF) 3b, ORF 6, and N proteins inhibit the expression of IFN-β (Zuo et al. 2020).

Among all interferons, IFN-β is the most compelling antiviral and anti-inflammatory agent that can result in significant clinical benefits. IFN-β can boost up immune response along with down-regulating the overexpressed IL-6 and IL-8 (Hung et al. 2020).

Shahabinezhad et al. designed a systems biology study to introduce therapeutic approaches for COVID-19 based on the dynamics of interferon-mediated immune responses (Mosaddeghi et al. 2020). They considered the underlying mechanisms of SARS mortality regarding age, along with vital signaling pathways activated by the virus. Subsequent literature review on COVID-19 and the other closely related



Heterogeneity chi-squared = 0.55 (d.f. = 2), $P = 0.761$

I-squared (variation in ES attributable to heterogeneity) = 0.0%

Fig. 2 Effects of interferon β-1 therapy in COVID-19 patients

viruses confirmed the results. They showed a definite relationship between the innate immune response threshold and mortality rate in COVID-19. Moreover, they attributed differences in the COVID-19 mortality rate between different ages to differences in the dynamics of interferon-related innate immune responses among children, adults, and the aged people. Consequently, a higher threshold of interferon response in old ages leads to a higher mortality rate among aged patients. Conversely, early induction of innate immunity and interferon in children results in lower mortality in them. Conclusively, they predicted that administration of interferon or interferon-inducing agents in the early stages of the disease can reduce mortality. This study also suggested that the addition of interferon-γ to an interferon type I, as a synergistic combination therapy, may increase its therapeutic benefits. Likewise, in vitro investigations represented the antiviral potential of INF-β against SARS-CoV-2 (Yuan et al. 2020).

It has been documented that lopinavir-ritonavir is beneficial in improving the clinical symptoms and reducing mortality rate (Irvani et al. 2020). In addition, they appeared to be more beneficial in combination with IFN-β.

Zuo et al. performed a retrospective study on the efficacy of lopinavir/ritonavir in combination with INF-α on hospitalized COVID-19 patients in Anhui, China (Zuo et al. 2020). They reported that early administration of IFN-α in combination with lopinavir/ritonavir may result in a shorter duration of SARS-CoV-2 shedding. Besides, some other clinical trials and case reports showed promising effects of IFN-α on decreasing blood levels of cytokines and virus clearance (Zhou et al. 2020), as well as improving clinical conditions (Xie et al. 2020). Zheng et al. demonstrated that although both IFN-α and IFN-β are beneficial in inhibition of Sars-CoV-2 infection and replication, IFN-β is a more potent antiviral drug against SARS-associated coronavirus than IFN-α (Zheng et al. 2004)

Considering the results of all mentioned studies, it seems that INF-β therapy can shorten the duration of hospital stay and decrease the mortality rate. Furthermore, no significant adverse effects or IFN-β drawbacks were reported. On the other hand, some vital interventions/medications may hinder the adverse reactions of IFN-β since more adverse effects were reported among IFN-β consuming MS patients (Zhou et al. 2020). It is noteworthy that clues could arise from INF-β therapy for developing an effective therapeutic strategy against COVID-19.

We might highlight that earlier administration of IFN (within 7 days from the onset of symptoms) could improve the efficiency. Possibly, combining IFN-β with two or more antiviral drugs in the first days of virus shedding may result in fast suppression of high initial viral load, improve the antiviral response, and consequently lead to more beneficial impacts.

Thereafter, timely administration of the drugs is highly suggested. Further studies are required to determine the golden time for IFN-β administration.

It has been suggested that intravenous injection of IFN-β can cause the drug to reach the endothelium faster; this might be more efficient for extra severe cases of COVID-19 (Mosaddeghi et al. 2020).

Treatment with injected or nebulized IFN-β may be favorable for the patients with auto-antibodies (Auto-Abs) against type I IFNs. It is noteworthy that severity of COVID-19 was attributed to neutralizing Auto-Abs against IFN-α and IFN-ω among 10% of patients. Therefore, it has been suggested that treatment with IFN-α may not be efficient due the aforementioned phenomenon (Bastard et al. 2020).

On the other hand, corticosteroids have been widely prescribed for COVID-19 patients (Arabi et al. 2020). However, the antagonist effects of corticosteroids should be considered seriously. Monfared et al. reported the increased adjusted odds ratio considering corticosteroids. It was previously reported that glucocorticoids inhibit signaling of IFN-β as well as most of the cytokines in human lung to the critical care settings. It is highly suggested to avoid using glucocorticoids at the early phases of severe COVID-19 or any viral-induced ARDS (Jalkanen et al. 2020). On the other hand, glucocorticoids are well known to be immunosuppressive; hence, it could be assumed that co-administration of INF and corticosteroids may dropdown the efficiency of IFN and have harmful effects as well. So the appropriate time of administration of both drugs requires further investigations.

The effect of interferon in the study by Fan-Ngai Hung et al. was more obvious in terms of reducing mean hospitalization days and mortality. In addition, since their study was a multicenter trial and had a higher sample size, the effective therapeutic capacities of interferon are better confirmed. These bolder effects can be attributed to the absence of hydroxychloroquine in the study, type of interferon-beta (IFN-β-1b), and different races, which should be considered and further investigated in future studies.

Limitations

Although some studies lacked control groups and had a small sample size, there were large controlled trials confirming the therapeutic effects of IFN-β-1a in COVID-19. On the other hand, the COVID-19 is a recent emerging disease, and the number of studies is not sufficient. Furthermore, the participants were not proportionate and were primarily male; however, it may be justified as being male is a risk factor for COVID-19 infection and also the selection of patients were random.

All the mentioned studies applied IFN-β-1a except the research by Fan-Ngai Hung et al., which employed IFN-β-1b. Indeed, IFN-β-1a and IFN-β-1b are recombinant preparations of IFN-β. The main difference between them is related to their production origin, whereas interferon-beta-1a is produced by mammal cells, while interferon-beta-1b is produced in modified *Escherichia coli*. Slight differences exist between these two recombinants in terms of glycosylation modalities and immunogenicity. To the best of our knowledge, no different major outcomes of these two forms in previous applications have been reported so far. However, Naghibi Irvani et al. designed a single-center, open-label, randomized, controlled, parallel-group, clinical trial to assess the differences between the efficacy of INF-β-1a and INF-β-1b in COVID-19 patients; and it is recommended that their results be considered in future studies (Irvani et al. 2020).

While three studies used hydroxychloroquine in combination with antiviral medications (lopinavir/ritonavir), Fan-Ngai Hung did not include hydroxychloroquine in their treatment protocols; this should be taken into account when interpreting the results. And it is noteworthy that the dosages of lopinavir/ritonavir were different among studies, whereas it was 200/50 mg P.O., two tablets QID for 5 days in Dastan et al. study (Dastan et al. 2020), 400/100 mg BD for 7–10 days in Monfared et al. study (Davoudi-Monfared et al. 2020), and 400 mg/100 mg every 12 h in Hung et al. study (Hung et al. 2020).

Despite the fact that all the studies were on severe patients with COVID-19, there were more critically ill patients admitted to the ICU in some studies; and this makes interpreting the results more difficult. Additionally, the impacts of comorbidities have been overlooked in these studies; future investigations should consider this issue.

It has recently been documented that the function of some ORF proteins (ORF6 and ORF3b) has been altered in SARS-CoV-2, which may change the pathogenesis mechanism of SARS-CoV-2 and its dealings with IFN-β.

It is noteworthy that IFNs dual role in SARS-CoV-2 replication leads to some clinical implications.

Although it was established that SARS-CoV-2 suppresses type I IFN signaling initially during infection, some evidence demonstrates that IFN-I responses are upregulated in severe stages of COVID-19 and induced expression of ISGs has been reported. Through initial stages of infection, viral nonstructural proteins (NSps) and ORFs suppress host IFNs and dysregulate ISGs with antiviral activities, while during later stages of infection, ISGs with pro-inflammatory and immunopathogenic potentials are activated (Park and Iwasaki 2020; Sa Ribero et al. 2020).

On the other hand, contradiction in interpretations in regard with IFN-I responses in patients with COVID-19 may attribute to different aspects in defining moderate, severe, and critical stages of COVID-19; different sampling time points; and different type of screening (assessing IFN-I itself or cellular responses to IFN-I) between studies. Consequently, extra

investigations on efficiency of IFN-I in mild compared with severe COVID-19 are essential to achieve a promising treatment for COVID-19 patients (Lee and Shin 2020).

Furthermore, due to the unknown nature of COVID-19 and a wide spectrum of symptoms and outcomes, more extensive interventions in different patients are needed to confirm the results; in addition, we attempted to present reliable results.

Conclusively, the results present INF-β as a promising and effective therapy for COVID-19. However, considering the limitations of the study, interpreting the results should be performed cautiously.

Conclusion

According to our findings, IFN-β is a promising innovative therapeutic option against COVID-19. Furthermore, early administration of IFN-β in combination with antiviral drugs demonstrated more promising results in treating COVID-19.

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Author contribution AN developed the original idea and protocol, interpreted the results, collected the data, and contributed to drafting all sections of the manuscript and language editing. HA contributed to the development of all sections of the manuscript, including data analysis, technical comment, electronic searching, data collecting and extracting, and interpretation. AF contributed to all sections of the manuscript development, technical comment, confirmation of extracted information, and interpretation.

Declarations

Ethics approval This study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences, Iran (code: TBZMED.REC.1399.015).

Competing interests The authors declare no competing interests.

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