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Current utilization of interferon alpha for the treatment of coronavirus disease 2019: A comprehensive review

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ABSTRACT

Recent studies have identified an association between perturbed type I interferon (IFN) responses and the severity of coronavirus disease 2019 (COVID-19). IFNα intervention may normalize the dysregulated innate immunity of COVID-19. However, details regarding its utilization and therapeutic evidence have yet to be systematically evaluated. The aim of this comprehensive review was to summarize the current utilization of IFNα for COVID-19 treatment and to explore the evidence on safety and efficacy. A comprehensive review of clinical studies in the literature prior to December 1st, 2021, was performed to identify the current utilization of IFNα, which included details on the route of administration, the number of patients who received the treatment, the severity at the initiation of treatment, age range, the time from the onset of symptoms to treatment, dose, frequency, and duration as well as safety and efficacy. Encouragingly, no evidence was found against the safety of IFNα treatment for COVID-19. Early intervention, either within five days from the onset of symptoms or at hospital admission, confers better clinical outcomes, whereas late intervention may result in prolonged hospitalization.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, took the world by surprise towards the end of 2019. The disease has greatly impacted healthcare systems, economies, and almost every aspect of our society. Through the endeavor of researchers worldwide, we now understand more about this disease, such as the primary routes of transmission of SARS-CoV-2, which include close contact, aerosols, and respiratory droplets. The virus enters human cells primarily by binding to angiotensin-converting enzyme 2 (ACE2) and initial spike protein priming by transmembrane protease, serine 2 (TMPRSS2) [1]. However, the heterogeneity of the prognosis of COVID-19 is still not well understood, as individuals may be entirely asymptomatic yet others may

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suffer from severe pneumonia, cytokine storm, and multiorgan failure [2].

2. Interferon alpha

While various therapeutic agents have been researched for treating COVID-19, there is yet a consensus for a treatment regimen. One therapeutic agent under investigation is interferon alpha (IFNα), a cytokine that is produced by the innate immune system in response to viral infection. IFNα is indicated for the treatment of various viral infections [3]. For example, IFNα is used for the treatment of hepatitis B and C virus (HBV and HCV) infections, condylomata acuminata due to human papillomavirus infection (HPV), and Kaposi's sarcoma due to human immunodeficiency virus (HIV) infection.

2.1. Mechanism of action for interferon alpha in a healthy individual

Endogenous IFNα production can be induced by interactions between pathogen-associated molecular patterns (PAMPs) and pathogen recognition receptors (PRRs), which are mediated by adaptors, tumor necrosis factor (TNF) receptor-associated factors, and IFN regulatory factors (IRFs) [4]. Two key transcription factors for IFN induction are IRF3 and IRF7. IRF3 is crucial for the initial induction of IFNα-1 and IFNβ, [5] whereas IRF7 subsequently amplifies IFNα and IFNβ production via a positive feedback loop. [6] Following phosphorylation, IRF3 and/or IRF7 dimerize, translocate to the nucleus, and induce type I IFNs and IFN-stimulated genes (ISGs) [7,8]. These IFNs then bind to IFN receptors, leading to the activation of Janus-kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathways, ultimately inducing the production of hundreds of different ISGs, some of which have known mechanisms related to antiviral activities [7–9].

2.2. Dysregulation of interferon alpha and interferon alpha-stimulating genes in COVID-19 patients

Recent studies have identified an association between a perturbed type I IFN response and COVID-19. The different degrees of disturbance in type I IFN response may explain the wide range of clinical observations and prognosis of the disease observed among COVID-19 patients. Exhibiting a normal or near-normal type I IFN response at the initial phase of infection seems to confer better outcomes in COVID-19 patients. As such, abnormal type I IFN responses are associated with worsening prognosis. This may also explain why younger individuals seem to be less affected by COVID-19. Higher concentrations of IFNα-2 and lower concentrations of proinflammatory cytokines, such as interleukin (IL)− 6 and TNFα, were observed in the plasma of COVID-19 survivors compared to non-survivors [10]. Severe and critically ill cases were reported to have lower concentrations of IFN-α2 in blood, which decreased with time and the severity of COVID-19 [11]. Furthermore, patients with inborn errors in type I IFN immunity or autoantibodies against type I IFNs are predisposed to life-threatening COVID-19 [12,13]. In addition to IFNs, attenuation of ISGs such as MX1 were also found to be downregulated in critically ill COVID-19 patients [11].

Clearly, these findings suggest that deficiency and dysregulation of IFN and ISG expressions are a signature of COVID-19 [14]. In an investigation to elucidate the mechanisms of SARS-CoV-2 infection, the production of ISG proteins was shown to be dose-dependent to type I interferons in primary human nasal epithelial cells, [15] suggesting that IFNα intervention may normalize the dysregulated innate immunity at the early phase of COVID-19 infection prior to the occurrence of a cytokine storm [16]. Although IFNα treatment has been reported in publications and implemented as the national treatment guidelines in some countries, [17–19] details regarding its utilization and therapeutic evidence have yet to be systematically evaluated. This review aimed to systematically investigate the current utilization as well as the latest evidence of the safety and efficacy of IFNα treatment for COVID-19.

3. Comprehensive review of the literature on the safety and efficacy of interferon alpha treatment in COVID-19 patients

In order to obtain a complete understanding of IFNα treatment in COVD-19 patients, we performed a systematic literature search according to the standards based on the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis as well as the Preferred Reporting Items for Systematic Reviews and Meta-analysis Extension for Scoping Review (PRISMA-ScR) guidelines. This ensured that a comprehensive and unbiased body of research could be procured for this review. The process of our literature search can be found in Supplemental ^{1}A–^{1}E. The final protocol was registered with the Open Science Framework on July 14th, 2021 (https://osf.io/g5fvb).

3.1. Summary of relevant literature

A total of 178 studies were found to have reported IFNα treatment for COVID-19 (Supplemental 2). [13,17,19,21–196] There were 64 case reports/series, 54 retrospective/prospective cohort studies, 20 case-control studies, 15 clinical trials, 18 cross-sectional studies, 4 registry studies, 2 longitudinal studies, and 1 multinational network cohort study. The subject inclusion dates were between December 15th, 2019, and March 25th, 2021. Polymerase chain reaction (PCR) methods were used by most studies to confirm a COVID-19 diagnosis. These studies were conducted in 14 countries (Argentina, Brazil, China, Cuba, France, India, Iran, Malaysia, Qatar, Russia, South Korea, Turkey, the United Arabs Emirates (UAE), and the United States of America (USA)). Most of the studies originated from China in our comprehensive review. Note that the possibility of IFNα treatment being used for another indication could not be ruled out in 2 publications due to the study design [103, 114]. In China, most of the reports of IFNα use came from Hubei and Zhejiang provinces.

3.2. Routes of administration of interferon alpha

The route of administration (ROA) of IFNα treatment included inhalation or nebulization (145), subcutaneous injection (10), intramuscular injection (2), intravenous injection (1), a combination of inhalation and injection (2), injection without reported site (9), nasal drops (1), and spray (1), or was not reported (7) (Table 1).

IFNα inhalation is part of the standard treatment in China, [18] and hence most studies reporting the use of IFNα inhalation came from China. Other studies using IFNα inhalation included Argentina, Qatar, and Russia. Subcutaneous injection of IFNα was reported in China, France, India, Turkey, the UAE, and the USA. Intramuscular injection was only reported in Cuba, which is part of their national standard treatment [17]. Wide ranges in the severity of COVID-19, age, timing of treatment initiation, and duration of treatment were observed in these studies (Table 2). Additionally, one study stood out because it evaluated the prophylactic efficacy and safety of IFNα nasal drops against COVID-19 in hospital workers [95].

3.3. Interferon alpha inhalation/nebulization

Inhalation/Nebulization was the most commonly reported ROA, as it is part of the national guidelines in China and was frequently reported in studies conducted by Chinese researchers. The safety of IFNα inhalation was demonstrated in two studies, which reported no difference in the proportion of COVID-19 patients receiving IFNα treatment between those with and without delayed-phase thrombocytopenia nor between survivors and non-survivors. [28,36] Furthermore, IFNα inhalation seemed to have beneficial effects on the liver during COVID-19 infection. One retrospective cohort study showed an association between IFNα inhalation and lower risks of elevated alanine aminotransferase

Table 1
Summary of interferon alpha treatment by route of administration. [13,17,19,21–196].

Route of administration	Number of publications	Patients receiving IFNα treatment*	Severity at initiation of treatment	Age range	Time from onset of symptoms to IFNα treatment	Dose and frequency	Duration
Inhalation	145	10,546	Asymptomatic to critical	35 days-91 years	1–47.8 days	0.1 MIU 4 times daily to 6 MIU 2 times daily	1–63 days (at most)
Subcutaneous	10	288	Asymptomatic to critical	20–83 years	2–12 days	IFNα:3 MIU/time, qodPegylated IFNα: 1–1.5 μg/kg (based on body weight)45–180 μg/dose/week (fixed dose)	IFNα:16 daysPegylated IFNα: 1–4 doses (around 1–4 weeks)
Intramuscular	2	2165	Asymptomatic to moderate	0–101 years	0–24 days	3 MIU, 3 times per week	2–4 weeks
Intravenous	1	Not reported	Moderate and severe	23–57 years	1–41 days	Not reported	Not reported

Note: IFNα: interferon alpha; MIU: million international units *For studies suspected to have repeated subjects, the study with the lower number was removed.

(>40 U/L) in patients aged between 32 and 56 with (n = 86) and without nonalcoholic fatty liver disease (n = 194) [60]. Another cross-sectional study investigating 342 patients of a similar age range also reported that IFNα inhalation was associated with reduced risks of abnormal liver function [125]. These seemingly beneficial impacts of IFNα on the liver are somewhat intriguing, given that liver toxicity is a noted side-effect of IFN-α2. In addition, IFNα inhalation may be associated with an abnormal triglyceride-glucose index and insulin resistance (n = 64) [32].

As the most commonly reported ROA, what we know about the efficacy of IFNα treatment for COVID-19 disease mainly came from the experiences of IFNα inhalation. An observation that we continued to see throughout the literature was the effect of the timing of IFNα treatment, wherein early initiation of treatment (within 5 days from onset of symptom) seemed to confer favorable outcomes, whereas late initiation of treatment may have been ineffective or may have resulted in unfavorable outcomes. Another observation was that mild and moderate patients seemed to respond better to IFNα treatment, whereas quite rarely were severe patients reported to have favorable outcomes following IFNα treatment. Both the timing of treatment and the severity of patients are two important factors that should be considered. Two reports on the same cohort of 77 moderate patients showed favorable associations between IFNα inhalation and lower chest computed tomography scores, lower number of CD8 + T cells, lower serum IL-6, TNF and c-reactive protein concentrations, and shorter duration from the onset of symptoms to viral clearance; however, the timing of treatment initiation was not reported [175,176]. A case-control study presented varying results on the effects of IFNα inhalation in reducing viral shedding time and the length of hospitalization [52]. Patients treated with IFN-α2b inhalation had significantly shorter viral shedding time and hospitalization; however, statistical significance was lost after applying the propensity score matching method. Treatment was initiated for the IFNα group (which consisted of 41 mild, 22 severe, and 5 critically ill patients) at a median of 5 days (Q1-Q3: 3–8), and no difference in the timing of treatment initiation was found when compared with the control group. Another retrospective cohort study showed that late IFNα inhalation (>5 days after admission) in a cohort mostly consisting of moderate patients was associated with late recovery [130]. Another retrospective cohort study compared the therapeutic efficacy of IFN-α2b inhalation (n = 44), IFN-α2b inhalation + lopinavir/ritonavir (n = 67), and control (n = 12) in COVID-19 patients with different severities [189]. The study found no differences in treatment methods with SARS-CoV-2 RNA clearance or with the duration of oxygen support. However, IFN-α treatment in those patients was initiated at a median of 6 days from the onset of symptoms, which may have been the reason for the non-significant difference. The combination of patients suffering from different severities may have also influenced the outcome, although there was no difference in the proportion of severities between the cohorts.

Evidence of the inefficacy of IFNα inhalation was only observed in studies that reported treatment initiated 5 days or later from the onset of symptoms. The timing of IFNα inhalation seemed to play a role in determining the prognosis and the outcome of treatment. The majority of studies that compared early and late administration of IFNα inhalation favored early administration, which was associated with positive outcomes. A retrospective cohort study showed that early administration (n = 216) within 5 days of hospital admission was associated with reduced mortality [130]. Administration within 5 days of the onset of symptoms was also correlated with a shorter viral clearance time [86]. A shorter duration of viral shedding was reported in a case-control study in 89 non-severe and 13 severe COVID-19-infected healthcare workers who received early IFNα inhalation within 5 days of the onset of symptoms [88]. Similarly, in a cohort of 852 patients who received IFNα inhalation at a median of 5 days from the onset of symptoms to admission, researchers found lower risks of disease progression, a shorter time from the onset of symptoms/admission to a negative nucleic acid test, and a shorter hospitalization time compared with patients who did not receive IFNα therapy [152]. A case-control study that included 147 non-severe and 34 severe patients analyzed these patients according to prolonged viral shedding time (n = 65; 21–39 days) or short-term shedding time (n = 116; 5–20 days) and discovered that a greater proportion of patients had received early IFNα inhalation in the latter group. [179] While the study found that early IFNα inhalation was associated with a faster recovery, it also identified that delayed antiviral treatment, including IFNα inhalation, was an independent factor associated with prolonged viral shedding time [179]. In contrast, a retrospective study showed that no matter whether the treatment was initiated within 7 days of symptom onset or not, there was no difference between the IFNα (n = 494) and non-IFNα (n = 152) groups in terms of the time from admission to discharge, intensive care unit (ICU) admission, invasive mechanical ventilation, or mortality [137].

3.4. Subcutaneous interferon alpha injections

Subcutaneous injection of IFNα was investigated in two clinical trials and a retrospective cohort study, providing stronger evidence of the safety and efficacy of IFNα treatment. The first clinical trial was a phase II randomized controlled trial that evaluated whether an additional single dose of pegylated IFNα (1 μg/kg) could provide extra benefits in comparison to the standard of care alone [98]. The trial reported that a greater proportion of subjects in the treatment group (19/20) compared with the control group (13/19) exhibited clinical improvement at day 15, as assessed by the WHO Ordinal Scale for Clinical Improvement. Similarly, a greater proportion of subjects in the treatment group (16/20) compared with the control group (12/19) achieved a negative PCR test at day 7. Although the clinical trial reported evidence supporting the use of subcutaneous pegylated IFNα injection for the treatment of COVID-19, it should also be noted that the sample size was small and possibly underpowered. Following the previous clinical trial, a phase III randomized controlled trial continued the investigation with a

Table 2
Evidence of safety and efficacy of interferon alpha treatment with corresponding qualitative score and percentage after critical appraisal.

Author	Publication year	Study type	Route of administration	Severity	Direction of evidence* for			Timing of trt initiation	Qualitative score	Percentage	Reference
					Safety	Efficacy	Early trt				
Bhushan	2021	Clinical trial	Subcutaneous	Moderate	+	+			9/13	69%	[181]
Chen FF	2020	Case-control	Inhalation	Severe	+				10/10	100%	[28]
Chen M	2021	Longitudinal	Inhalation	Mild-Critical	–				8/8	100%	[32]
Chen T	2020	Case-control	Inhalation	Mild-moderate	+				8/10	80%	[35]
Chen WX	2020	Case-control	Inhalation	NR	+				9/10	90%	[36]
Gong	2021	Retrospective cohort	Inhalation	Severe		–			9/10	90%	[46]
Hao	2020	Retrospective cohort	Inhalation	Mild-Critical		+ /-			10/10	100%	[53]
Huang R	2021	Cross-sectional	Inhalation	Mild-Severe		+	+	Within 5 days of admission	6/7	86%	[187]
Huang R	2020	Retrospective cohort	Inhalation	Non-severe-Severe	+				10/10	100%	[61]
Li C	2021	Clinical trial	Inhalation	Moderate-Severe	+	+			9/13	69%	[67]
Li H	2021	Retrospective cohort	Inhalation	Mild-Severe		–			10/10	100%	[70]
Li LZ	2020	Case-control	Subcutaneous	NR	+				10/10	100%	[73]
Li X	2021	Retrospective cohort	Inhalation	Severe-Critical		–		Within 4 days of admission	9/10	90%	[188]
Liu D	2020	Case-control	Inhalation	Moderate-Critical		+ /-			10/10	100%	[84]
Liu JY	2020	Retrospective cohort	Inhalation	NR		+	+	Within 5 days of onset	10/10	100%	[87]
Liu JY	2021	Retrospective cohort	Inhalation	Mild-Severe		–			8/10	80%	[189]
Liu W	2020	Case-control	Inhalation	Mild-Severe		+	+	Within 5 days of onset	10/10	100%	[89]
Meng	2021	Clinical trial	Nasal drops	NA	+			Prophylaxis	7/9	78%	[96]
Ozcifci	2021	Cross-sectional	Subcutaneous	NA	+			Prophylaxis	6/8	75%	[190]
Pandit	2021	Clinical trial	Subcutaneous	Moderate	+	+			9/13	69%	[99]
Pereda	2020	Prospective cohort	Intramuscular	Asymptomatic-Moderate		+	+	Asymptomatic: treated on the day	8/10	80%	[103]
Pereda	2020	Retrospective cohort	Intramuscular	Asymptomatic-Moderate		+	+	of positive PCRSymptomatic: average of 2 days after diagnosis	8/10	80%	[17]
Rao	2020	Retrospective cohort	Intravenous	Moderate-Severe		+			10/10	100%	[107]
Wang B	2020	Retrospective cohort	Subcutaneous	NR		+ /-	+	Within 3 days of admission	9/10	90%	[123]
Wang J	2021	Cross-sectional	Inhalation	NR	+ /-				8/8	100%	[126]
Wang N	2020	Retrospective cohort	Inhalation	Asymptomatic-Critical		+ /-	+	Within 5 days of admission	10/10	100%	[131]
Wong	2021	Retrospective cohort	Inhalation	Mild-Critical		–	–	Within 7 days of onset of symptoms	10/10	100%	[138]
Yin	2021	Retrospective cohort	Inhalation	Moderate		+	–	Within 7 days of onset of symptoms showed no benefits	9/10	90%	[193]
Yu J	2020	Retrospective cohort	Inhalation	NR		+	+	Within 5 days of admission	10/10	100%	[153]
Zheng F	2020	Clinical trial	Inhalation	Moderate-Severe	+	+			9/13	69%	[169]
Zhou Q	2020a	Retrospective cohort	Inhalation	Moderate		+			10/10	100%	[176]
Zhou Q	2020b	Retrospective cohort	Inhalation	NR		+			10/10	100%	[177]
Zhou X	2021	Case-control	Inhalation	Severe		–			8/8	100%	[195]
Zuo Y	2020	Case-control	Inhalation	Mild-Severe		+ /-	+	Within 5 days of onset of symptoms	10/10	100%	[180]

Note: trt: treatment; NA: not applicable; NR: not reported *The "+ " sign indicates evidence that favors; the "-" sign indicates evidence agains

similar study design in larger groups of patients, including 120 participants receiving a single dose of pegylated IFNα (1 μg/kg) in addition to standard of care; 130 participants received standard of care only [181]. The trial reported that a greater proportion of subjects in the treatment group (90/112) compared with the control group (75/110) exhibited clinical improvement at day 8, as assessed by the WHO Ordinal Scale for Clinical Improvement. Similarly, a greater proportion of subjects in the treatment group (103/113) compared with the control group (86/109) achieved a negative PCR test at day 7.

A retrospective cohort study included 19 patients who received IFNα

injections until their PCR test returned a negative result, in addition to lopinavir/ritonavir tablets (400 mg/time, bid) for 10 days; [122] the control group received lopinavir/ritonavir alone (n = 22). That study reported that patients receiving combination therapy spent an average of 16 days in hospital, which was significantly shorter than patients in the control group, who spent an average of 23 days in hospital. Furthermore, a subgroup analysis found that early administration of IFNα (within 72 h following admission) resulted in an even shorter hospital stay of 10 days compared with late administration (after 72 h following admission). In other words, there was apparently no difference in terms of days of hospital stay between patients administered IFNα and patients receiving lopinavir/ritonavir alone if IFNα was administered 72 h or later after admission. Although this study reported a longer time from the onset of symptoms to hospital admission (a mean of 12 days), the large standard deviation and a relatively smaller sample size could have affected the average value (and hence reporting the median value would be a better option when outliers exist in data).

3.5. Intramuscular interferon alpha injections

Intramuscular injection of IFNα is the national treatment standard in Cuba, which was reported in two cohort studies, one being an updated report of the other previous study [17,102]. Mild (and possibly moderate) patients received IFNα injection (3 MIU, three times per week) for a maximum of 4 weeks, in addition to other antiviral regimens such as oseltamivir plus azithromycin or lopinavir/ritonavir plus chloroquine. Patients who did not receive IFNα injection due to contraindications or unwillingness served as comparators in the studies. Moreover, these studies implemented early treatment. The first study reported the initiation of IFNα treatment within 5 days of the onset of symptoms, while in the updated report, more patients received even earlier treatment within an average of 2 days after the onset of symptoms. The updated publication respectively reported 1958 (99·0%) and 64 (49·6%) patients discharged from the hospital in the IFNα-treated and comparator groups. The IFNα-treated group also had a lower proportion of ICU admissions and a lower case fatality rate in those admitted to the ICU.

3.6. Other routes of administration for interferon alpha treatment

Intravenous injection of IFNα was reported in one retrospective cohort study investigating the effects of bodyweight on the clinical outcomes of COVID-19 [106]. That study showed that IFNα was associated with reduced mortality in overweight patients. In another study, a formulation of IFNα nasal drops was evaluated as a prophylactic measure against COVID-19 [95]. A case study of a 69-year-old female patient who traveled from the US to China was found positive for SARS-CoV-2 RNA during routine screening and subsequently received IFNα-2b spray and other drugs for treatment [185].

3.7. Other interferon alpha-related formulations

Several IFNα-related formulations were found to have been applied as a COVID-19 treatment. One formulation was a recombinant version of IFNα with a modified spatial configuration named recombinant supercompound IFN (rSIFN-co), which was reported to have 20 times stronger antiviral activity [66]. The formulation was evaluated and compared to traditional IFNα via nebulization in 83 moderate and 11 severe patients from 14·0–14·5 days (median) of the onset of illness. The rSIFN-co group displayed faster clinical improvement, radiological improvement, and viral nucleic acid negative conversion rates. Another formulation named novaferon was a non-natural protein created using modified DNA shuffling technology, which demonstrated more than 10 times higher antiviral potency compared to IFNα-2b [196]. Novaferon inhalation was associated with a greater rate of and shorter time to SARS-CoV-2 clearance.

3.8. Treatment in COVID-19 patients with comorbidities

The use of IFNα inhalation was reported in patients with various comorbidities and conditions, including patients with atopic dermatitis, [38] allergic rhinitis, [38] bronchiolitis, [25] chronic obstructive pulmonary disease, [84,162] tuberculosis, [55] cardiovascular disease, [22] hypertension, [22,84,150,162] diabetes, [32,39] hyperlipidemia, [150] obesity, [126] metabolic syndrome, [192] chronic hepatitis B infection, [76,153] chronic kidney disease, [22,70] malignancy, [163] liver transplant, [50] kidney transplant, [70,172] and pregnancy. [19] The use of subcutaneous injection of IFNα was reported in patients with diabetes, [42] hypertension, [42,44] hyperlipidemia, [42] chronic hepatitis B infection, [140] primary myelofibrosis with macrocytic anemia, [44] dementia, [44] chronic kidney disease, [44] Behcet's disease, [190] and osteoporosis. [44] However, whether IFNα treatment is safe and efficacious in COVID-19 patients with these comorbidities requires further clinical studies.

4. Interferon alpha treatment for COVID-19 patients in the current context

4.1. Early administration of interferon alpha confers clinical benefits compared with late administration

We found no evidence against the safety of IFNα treatment for COVID-19 patients, although consistent evidence suggests that early administration confers clinical benefits, in contrast to late administration which may deteriorate the state of COVID-19. One important aspect regarding IFNα therapeutics for COVID-19 is the timing of treatment initiation. Our current understanding of COVID-19 management, in light of IFNα, supports the theory of early immune-stimulation enhancing antiviral activity and late immunosuppression ameliorating a cytokine storm. [2] Early initiation of IFNα treatment confers clinical improvement by enhancing antiviral responses and limiting viral infection, whereas late initiation may aggravate the cytokine storm and deteriorate the situation. This was commonly evaluated by the duration from the onset of symptoms to the time of hospital admission or treatment initiation. Fairly consistent evidence supports this hypothesis, no matter whether the treatment was via inhalation, subcutaneous injection, or intramuscular injection. [17,86,88,102,122,130] Studies reporting inefficacy of IFNα or delayed hospital discharge also reported a longer time from the onset of symptoms to hospital admission. [46,69] Based on these studies, we believe that the magic number is five. Treatment initiated within five days of the onset of symptoms may be considered as early treatment, which confers a better treatment response and prognosis. As such, treatment initiated earlier than 5 days from the onset of symptoms may be even more favorable.

4.2. Severity of COVID-19 disease as a key determinant

The severity of disease seems to be another key determinant of IFNα treatment. Patients with severe COVID-19 disease did not seem to benefit from IFNα treatment [46,188,195]. On the contrary, a case report from the UAE suggested clinical benefits of IFNα treatment in severe patients, in which three cases received subcutaneous injections of pegylated IFNα-2a following clinical deterioration and oxygen support. [42] The timing of treatment initiation of the three reported cases were 3, 7, and 11 days after hospital admission. These male patients were respectively 61, 37, and 38 years of age. This case report serves as one of the few pieces of evidence that supports the use of IFNα in severe COVID-19 patients, two of which could be regarded as late administration. Another case report from China reported a 47-year-old male who received IFNα inhalation 7–8 days after the onset of symptoms and was discharged from the hospital after 10 days of treatment. Nevertheless, the majority of the literature that reported IFNα treatment in severe COVID-19 cases usually stated unfavorable outcomes. With less

controversy, IFNα treatment showed efficacy in moderate patients, as shown in cohort studies [176,193] and clinical trials [98,181]. Overall, no alarming findings on the safety of IFNα agents were found in this review; however, late administration of IFNα beyond 5 days after the onset of symptoms or hospital admission is not suggested.

The theory that supplementing patients with exogenous IFNα could induce a stronger immune response required to fight COVID-19 is supported by clinical findings such as the higher concentrations of IFNα-2 observed in the plasma of COVID-19 survivors and lower concentrations of IFNα2 reported in the blood of severe and critically ill cases. Not only does COVID-19 induce a state of interferon deficiency, but the associated inflammation also impairs the efficacy of endogenous IFN-α2 by interfering with IFN-signaling via the JAK-STAT signaling pathway and degrading the IFN receptor. Early administration of IFNα is also recommended due to the large body of evidence supporting early administration of IFNα inhalation, no studies reporting detriments of early administration, and evidence of unfavorable outcomes in patients who received late administration. Moreover, the burden of COVID-19-induced inflammation is at its lowest in the initial stage of the disease. In addition, most of the publications in this review used inhalation as the ROA, which is likely the most direct method, although other ROAs could also be as beneficial or even more favorable to avoid respiratory complications and provide convenience in clinical practice.

4.3. Co-administration of interferon alpha with other drug treatments

Often the treatment and management of COVID-19 in the literature reported multiple therapeutic agents and methods. Given the global state of the COVID-19 pandemic, a multi-drug and multi-pronged approach is indeed warranted. For example, JAK1/2 inhibitors have been suggested for the treatment of COVID-19 patients, either as a monotherapy or a combination therapy with IFNα [197]. Other potential drugs that could be used in combination with IFNα include statins and hydroxyurea, both of which may lower the levels of circulating inflammatory cytokines and facilitate in reducing the cytokine storm observed in COVID-19 patients [197]. However, combination treatment makes it difficult in clinical studies to elucidate the safety and efficacy of these compounds. Furthermore, possible drug-drug interactions may also pose a risk of poor prognosis. A couple of studies reported the use of IFNα inhalation and ribavirin, which showed results against the use of such a combination. A retrospective cohort study investigating 208 severe patients showed that there were no differences in clinical improvement, nucleic acid negative conversion, length of hospitalization, survival time, or mortality between the 29 patients who received IFNα inhalation and ribavirin and the 179 patients who received ribavirin alone [46]. Furthermore, a larger retrospective study investigating 1074 non-severe and 963 severe patients found that IFNα inhalation in combination with ribavirin was associated with higher risks of hospital stay over 15 days [69]. These studies suggest possible drug-drug interactions between IFNα and ribavirin. Note also that both aforementioned retrospective cohort studies had a longer time from the onset of symptoms to admission: a median of 13 days in the former study and a median of 8 days in the latter study. Thus, the influence of the time of the initiation of IFNα treatment cannot be ruled out.

4.4. Prophylaxis with interferon alpha

Individuals with a perturbed IFN response, inborn errors in type I IFN immunity, or autoantibodies against type I IFNs are predisposed to life-threatening COVID-19 [12,13]. It then raises speculations on what would happen if the opposite were to occur, i.e., increase IFN concentrations prior to COVID-19 infection. The question of whether IFNα prophylaxis prevents COVID-19 infection is worth examining. A single-center study in China recruited 529 high-risk and 2415 low-risk medical personnel who received 2–3 drops/nostril/time four times daily of IFNα for 28 days with or without subcutaneous injections of thymosin-α1 [95]. During the study period, no medical personnel were infected with COVID-19. In contrast, the control group, who did not receive IFNα, from external sources during the same period in the same province recorded 1716 confirmed cases among 3387 medical personnel. Another piece of evidence came from the observation of patients with Behcet's syndrome in Turkey [190]. Behcet's syndrome is a rare inflammatory disorder that results in a wide range of signs and symptoms and can be treated with IFNα. Using univariate logistic regression, the researchers analyzed data from 1037 patients and found that patients on IFNα treatment had an odds ratio of 0.12, meaning that they were 88% less likely to contract COVID-19 disease. It should be noted though that the number of patients on IFNα treatment was relatively small.

5. Further considerations of this review

To the best of our knowledge, this is the first and most updated review that provides a clear and comprehensive summary of the global utilization of IFNα treatment for COVID-19. We expansively searched for reports of IFNα treatment in the publications written in English and Chinese prior to December 1st, 2021. However, some considerations should be noted. While the timing of IFNα treatment was important, this information was not always reported in the literature. Furthermore, although we identified 34 publications that reported statistics relevant to the safety and efficacy of IFNα treatment in COVID-19 patients (Table 2), not all of these studies were designed for this purpose, and careful interpretations of their (and our) results are therefore necessary. There is also a lack of evidence on the associations between age and IFNα treatment as well as comorbidities and IFNα treatment. In fact, patients with comorbidities were often excluded from or not specified in the analyses identified in this review. These possible associations could be the focus of future studies.

Some observational studies inferred certain treatments were effective or ineffective against COVID-19; however, careful assessments and interpretations are necessary as some conclusions were drawn from data that lack comparability among cohorts and/or appropriate statistical methods. Age and comorbidities are two major risk factors for severe COVID-19, [198] which were often the disparities among patient groups in cohort studies. The application of simple statistics in these studies could lead to incorrect conclusions. To overcome this problem, matching or regression techniques could be applied, with the latter possibly being the better option [198].

To illustrate the issue in statistical analysis, we described here a case-control study [52] that compared outcomes between patients treated with and without IFNα inhalation, in which matched and unmatched datasets were used for multivariate cox regression analysis. In unmatched analysis, IFNα inhalation was associated with reduced ICU admission, viral shedding time, and length of hospitalization as well as increased discharge rate, whereas in matched analysis, no associations were found. Although both analyses were valid, applying the cox regression method to adjust for confounders may be sufficient to draw inference, whereas there may be a risk of losing statistical power when reducing sample sizes for the purpose of matching [198].

6. Recommendations for future studies on IFNα treatment in COVID-19

Through this review, we have generated a number of recommendations on the study design for future clinical researchers who wish to investigate IFNα treatment for COVID-19. Firstly, it may be worthwhile to record the severity of COVID-19 at both hospital admission and at treatment initiation as well as the worst severity during hospitalization, in addition to providing a clear definition of the grading system used. Secondly, as treatment for COVID-19 appears to be associated with the timing of treatment initiation, especially in the case of IFNα, we recommend that future studies report this information in relation to the

onset of symptoms and/or hospital admission. Thirdly, for reporting IFNα treatment, it would be useful to include more explicit details, such as dose, frequency, treatment duration, and ROA. Fourthly, various confounding factors (e.g., age) could affect outcomes. To adjust for these confounders, matched data and the propensity score method may be beneficial if a greater number of control samples (e.g., 1:2–4) is used, although a regression analysis could also suffice.

A number of unanswered questions warrant future research. For instance, we do not know the optimal timing and ROA for IFNα intervention, and we do not know if there is a certain subgroup of COVID-19 patients who may benefit the most from this treatment, and vice versa. We also do not know the cellular mechanisms of IFNα treatment for COVID-19. Whether different strains of COVID-19 respond differently to IFNα treatment is worthy of research. This was never reported in any of the relevant publications that we comprehensively reviewed. Finally, the efficacy of IFNα prophylaxis is yet to be clarified. These pieces of information may help elucidate and optimize the utilization of IFNα treatment in COVID-19.

We hope this review has shed some light on different aspects of the use of IFNα treatment for COVID-19. It has been said that the SARS-CoV-2 is here to stay; therefore, a further understanding of COVID-19 and an establishment of treatment and management for COVID-19 are of paramount importance for the future of mankind.

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CRediT authorship contribution statement

Ling-Ying Lu: Conceptualization, Data curation. **Po-Hao Feng:** Conceptualization, Validation, Writing – original draft, Writing – review & editing. **Ming-Sun Yu:** Conceptualization, Validation, Visualization, Writing – original draft. **Min-Chi Chen:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Alex Jia-Hong Lin:** Methodology, Data curation. **Justin L. Chen:** Methodology, Data curation, Writing – review & editing. **Lennex Hsueh-Lin Yu:** Conceptualization, Methodology, Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. .

Conflicts of interest

LHY and AJL are full-time employees of Panco Healthcare Co., Ltd. JLC is a contract researcher working for Panco Healthcare Co., Ltd.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alex Jia-Hong Lin, Justin L. Chen, and Lennex Hsueh-Lin Yu declare their employment status with Panco Healthcare Co., Ltd., a subsidiary of PharmaEssentia Corporation. LHY and AJL are full-time employees of Panco Healthcare Co., Ltd. JLC is a contract researcher working for Panco Healthcare Co., Ltd. Although these authors are affiliated with the industry, they declare that their contribution to this manuscript was not funded by their employer but rather driven by their passion in science and desire to contribute to the fight against the COVID-19 pandemic.

Data Avalibility

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.cytogfr.2022.01.001.

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