Infect Dis Ther (2022) 11:953–972
https://doi.org/10.1007/s40121-022-00633-9

REVIEW

Interferon Treatments for SARS-CoV-2: Challenges and Opportunities

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Received: March 4, 2022 / Accepted: March 31, 2022 / Published online: April 21, 2022

ABSTRACT

Interferon (IFN) therapies are used to treat a variety of infections and diseases and could be used to treat SARS-CoV-2. However, optimal use and timing of IFN therapy to treat SARS-CoV-2 is not well documented. We aimed to synthesize available evidence to understand whether interferon therapy should be recommended for treatment compared to a placebo or standard of care in adult patients. We reviewed literature comparing outcomes of randomized control trials that used IFN therapy for adults diagnosed with SARS-CoV-2 between 2019 and 2021. Data were extracted from 11 of 669 screened studies. Evidence of IFN effectiveness was mixed. Five studies reported that IFN was a better therapy than the control, four found no or minimal difference between IFN and the control, and two concluded that IFN led to worse patient outcomes than the control. Evidence was difficult to compare because of high variability in outcome measures, intervention types and administration, subtypes of IFNs used and timing of interventions. We recommend standardized indicators and reporting for IFN therapy for SARS-CoV-2 to improve evidence synthesis and generation. While IFN therapy has the potential to be a viable treatment for SARS-CoV-2, especially when combined with antivirals and early administration, the lack of comparable of study outcomes prevents evidence synthesis and uptake.

Keywords: SARS-CoV-2; COVID-19; Interferon

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Key Summary Points

Why carry out this study?

COVID-19 is a global pandemic, and effective therapies are needed to reduce the burden on the health system.

Interferon therapy may be effective in the clinical management of SARS-CoV-2 as interferons play an important role in immune response.

What was learned from the study?

Synthesizing existing data on interferon therapy for COVID-19 is challenging, as previous trials have used methods, outcome measures and interferon subtypes that vary greatly.

Standardized outcomes are needed in future studies to enable comparisons and draw conclusions about the effectiveness of interferon therapy in the treatment of COVID-19.

INTRODUCTION

When the World Health Organization (WHO) declared SARS-CoV-2 (COVID-19) a global pandemic, the race began to find therapies that prevent or reduce the impact and transmission of the virus. The WHO hypothesized that interferon (IFN) therapy could be a potential treatment for SARS-CoV-2 [1], as IFNs are naturally elevated in response to the onset of viral infections [2]. There are three main classifications of interferon, with multiple subtypes and distinct functions (Table 3). Interferon alpha, or IFN-α, has been the most researched subtype, and its immunomodulatory effects have been used to treat human papillomavirus, multiple sclerosis and cancer [2].

Interferons have been documented to play a role in the pathogenesis of SARS-CoV-2. Low levels of IFN-I and IFN-III have been found among patients infected with SARS-CoV-2 [3], and impaired IFN production has been associated with low viral clearance [4]. By contrast, another study examining patients with severe SARS-CoV-2 reported robust IFN-1 responses, suggesting an overexpression of innate antiviral defenses contributing to the pathogenesis of SARS-CoV-2 [5]. These discrepancies in the role of IFNs in SARS-CoV-2 expression may be related to the progression of SARS-CoV-2 at the time of intervention and may suggest the potential for different treatment outcomes when IFN therapies are administered at different disease stages. Studies in mice models support this suggestion; IFN therapy in mice has been effective in treating early-onset SARS-CoV-2 because of reduced innate antiviral defenses, while later-stage treatments exacerbated immune responses [6].

Although vaccinations have successfully reduced the transmission and onset of SARS-CoV-2 [7], breakthrough cases have been reported [7], and access to and uptake of vaccination remain low in many populations. In under-vaccinated groups, treatment for SARS-CoV-2 is as essential as prevention to reduce the risk and impact of transmission [6]. A review and evidence synthesis of interferon therapy for SARS-CoV-2 is currently absent from existing literature. A review to identify contradictions in existing data and support extrapolations about the appropriate type of interferon therapy during different stages of SARS-CoV-2 infection is urgently needed. Therefore, the objective of this review is to synthesize available evidence to understand whether interferon therapy should be recommended as a treatment option compared to placebo or standard of care for adult patients diagnosed with SARS-CoV-2 in any country.

METHODS

We rapidly reviewed literature on outcomes of randomized control trials (RCTs) that used IFN therapy for adults (in- and outpatients) diagnosed with SARS-CoV-2. We applied the PICOS (Population, Interventions, Controls, Outcomes

Table 1 Eligibility criteria for the PICOS

Criteria	Description/inclusion criteria
Population	Adult in- and outpatients with a positive SARS-COV-2 diagnosis in any country
Interventions	Interferon therapy inclusive of all subtypes (e.g., beta, gamma, lambda)
Comparators	Placebo
	Any standard of care
	Combination treatments
	Control groups
Outcomes	Any outcome, including but not limited to:
	Hospitalization
	Death
	Viral clearance
	Viral shedding
	Symptom resolution
Study Design	Randomized controlled trials (RCTs)
Language	English

and Study Designs) criteria for the research question for this review (Table 1).

Inclusion and Exclusion

Randomized control trials (RCTs) that investigated interferon as a therapeutic treatment to SARS-CoV-2 that were written in English were included. RCTs were excluded if interferon was used as a diagnostic tool or examined as an inflammatory response. All comparators were considered, including placebos or control groups, combination treatments and new drugs. There were no time limitations in the inclusion and exclusion criteria, as the majority of studies were published within the same time frame (2019–2021). This article is based on previously conducted studies and does not contain any new studies involving human participants or animals performed by any of the authors.

Study Identification

PubMed and Medical Literature Analysis and Retrieval System Online (MEDLINE) were used to identify studies. Keywords used included variations on: human patients, SARS-CoV-2 and interferon. Study protocols, pre-publications or unpublished studies were excluded.

Study Selection

A total of 669 studies met the initial screening criteria (Fig. 1). Two independent reviewers appraised abstracts to select studies for full-text screening (n = 132). Discrepancies between the two reviewers were resolved by discussion until a unanimous decision was made. Data were extracted from 11 studies including interferon types, subtypes, molecular mechanisms, SARS-CoV-2-related properties, therapy names and phases of testing, and patent ownership, as these were deemed most relevant to meet the objectives of the review.

RESULTS

Eleven studies met our inclusion criteria (Table 2). Findings on the benefits of IFN therapy for the treatment of SARS-CoV-2 were mixed. Five studies reported that IFN was a better therapy than the control, four found no/minimal difference between IFN and the control, and two concluded that IFN led to worse patient outcomes than the control.

High Variability of Outcome Measures

The studies included in our review contained highly variable outcome measures. Specifically, two studies measured time to viral clearance as their outcome of interest, while two others examined viral clearance after a specified time interval. Viral clearance was defined as one negative RT-PCR swab in one study, two negative swabs in two studies and a mid-turbinate swab in another study. Additionally, the day that viral clearance was measured varied greatly by study. The three studies measuring the

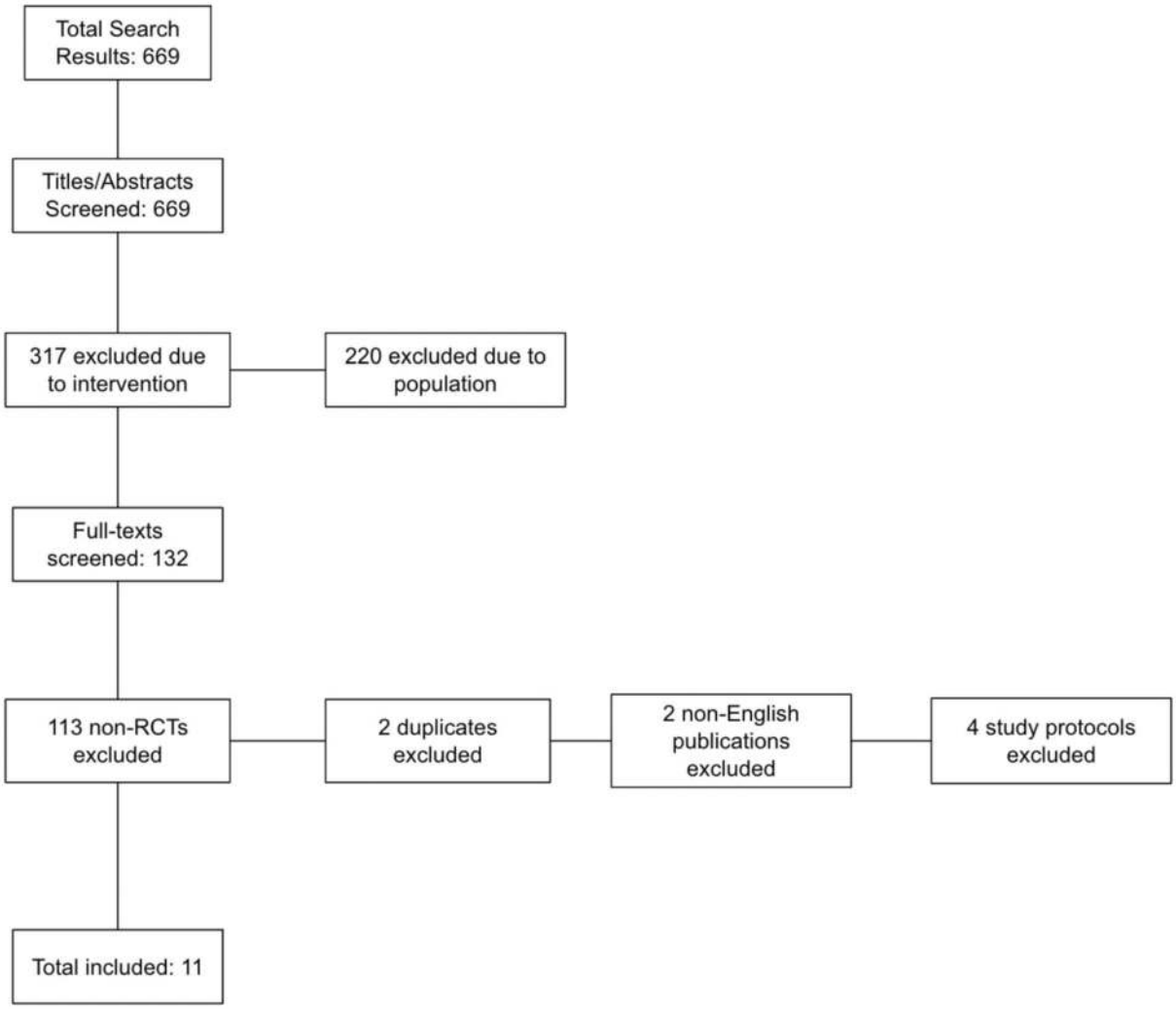

Fig. 1 Study identification, screening and selection process

proportion/number of individuals with viral clearance on a chosen day after symptom onset as their primary outcome all measured viral clearance on different days (i.e., 7, 9 or 28). A further three studies used time to clinical improvement as a primary outcome while two others used time to clinical response or time to clinical recovery. These definitions also varied greatly, with clinical response measured on a six-point ordinal scale and clinical recovery measured based on the initial recorded signs and symptoms of participants. All of the studies measuring clinical symptoms as a primary outcome used a different set of indicators, with some creating their own ordinal scales and others implementing the WHO Ordinal Scale for Clinical Improvement. One study measured duration of viral shedding cessation, and one measured in-hospital mortality at day 28.

High Variability of Intervention Type and Administration

The interventions included in our review also used various interferon subtypes in their analyses, which further limited comparability between studies. The most common type of interferon distributed was IFNβ-1b. IFN-β is a type I interferon produced by fibroblasts and is commonly used to limit the progression of

Table 2 Summary of findings to date on clinical trials investigating interferon therapies for the treatment of SARS-CoV-2

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
1	32,758,689	SARS-CoV-2 clearance in SARS-CoV-2 patients with novaferon treatment: A randomized, open-label, parallel-group trial [8]	89	(a) Novaferon (b) Lopinavir/ritonavir (c) Novaferon + lopinavir/ritonavir	Hospitalized SARS-CoV-2 patients clinically classified as moderate or severe	Viral clearance rate using RT-PCR at day 9: Arm C (lopinavir/ritonavir + novaferon) had the largest viral clearance rate at day 9 (13–18% more). *P*-value of lopinavir/ritonavir + novaferon vs. novaferon was 0.2839	1 center, Changsha City, Hunan Province, China
2	32,862,111	Interferon β-1b in treatment of severe SARS-CoV-2: A randomized clinical trial [9]	99	(a) Interferon-β 1b + hydroxychloroquine + lopinavir/ritonavir OR atazanavir/ritonavir (b) Treatment a except interferon-β-1b	Hospitalized patients with severe SARS-CoV-2	Time to clinical improvement was measured. This was significantly shorter in the IFN group (treatment a) compared to the control group (treatment b) [9(6–10) vs. 11(9–15) days respectively, p = 0.002]	1 center, Tehran, Tehran Province, Iran

Table 2 continued

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
3	33,264,556	Repurposed antiviral drugs for SARS-CoV-2—Interim WHO Solidarity Trial Results [1]	2050	(a) Remdesivir (b) Hydroxychloroquine (c) Lopinavir (d) Interferon-β-1a	Hospitalized patients	In-hospital mortality before or after day 28 Interferon: 243/2050 (12.9%) Control: 216/2050 (11.0%) Odds ratio of 16.8 and variance of 113.3 Rate ratio for death: 1.16 (0.96–1.39)	405 hospitals in 30 countries (Albania, Argentina, Austria, Belgium, Brazil, Colombia, Egypt, Finland, France, Honduras, India, Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania, Luxembourg, Malaysia, North Macedonia, Norway, Pakistan, Peru, Philippines, Saudi Arabia, South Africa, Spain, Switzerland)

Table 2 continued

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
4	33,620,016	Effect of a genetically engineered interferon-alpha versus traditional interferon-alpha in the treatment of moderate-to-severe SARS-CoV-2: a randomised clinical trial [10]	96	(a) Recombinant super compound interferon a (b) Interferon-alpha-2a or interferon-alpha-2b	Hospitalized patients diagnosed with moderate-to-severe SARS-CoV-2 pneumonia	Time to clinical improvement defined as the time from enrollment to an improvement of two points on a seven-category ordinal scale The primary outcome of the rSIFN-co group was statistically shorter than that of the interferon-alpha group (median, 11.5 days vs. 14.0 days; HR, 1.76; 95% CI, 1.10 to 2.81; p = 0.019)	5 centers, Wuhan City, Hubei Province, and Chengdu City, Sichuan Province, China
5	33,181,328	Randomized controlled open-label trial on the use of favipiravir combined with inhaled interferon beta-1b in hospitalized patients with moderate to severe SARS-CoV-2 pneumonia [11]	89	(a) Favipiravir + interferon beta-1b (b) Hydroxychloroquine	Hospitalized patients with moderate-to-severe SARS-CoV-2 pneumonia	Time from assignment to clinical recovery Arm (a) 7 days Arm (b) 7 days No significant difference	1 center, Muscat, Muscat Province, Oman

Table 2 continued

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
6	33,785,743	Peginterferon lambda-1a for treatment of outpatients with uncomplicated SARS-CoV-2: a randomized placebo-controlled trial [12]	120	(a) Peginterferon lambda-1a (b) Placebo	Asymptomatic and symptomatic patients, mild-to-severe progression	Duration until viral shedding cessation in days Arm a: 7 days (5–13) Arm b: 7 days (5–10) HR: 0.81 (0.56, 1.19) *P*-value = 0.29	1 center, California, USA
7	32,401,715	Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with SARS-CoV-2: an open-label, randomised, phase 2 trial [13]	127	(a) Lopinavir/ritonavir + ribavirin + interferon beta-1b (b) Lopinavir/ritonavir	Early onset of SARS-CoV-2; most patients admitted to hospital within 7 days of symptom onset	Time from start of study treatment to negative nasopharyngeal swab Combination: 7 days [IQR 5–11] Control: 12 days [8–15] Combination group had a significantly shorter median time HR 4·37 [95% CI 1·86–10·24], $p = 0.0010$	6 centers, Hong Kong, China

Table 2 continued

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
8	33,556,319	Peginterferon lambda for the treatment of outpatients with SARS-CoV-2: a phase 2, placebo-controlled randomised trial [14]	60	(a) Peginterferon lambda-1a (b) Placebo	Early-onset SARS-CoV-2 (diagnosed within 7 days of symptom onset or first positive test if asymptomatic)	Proportion of individuals with a negative mid-turbinate swab for SARS-CoV-2 at day 7 Treatment: 24 (80%) negative 19 (63%) negative $p = 0.15$ Unadjusted odds ratio for peginterferon lambda vs. placebo 2.32 (0.74–7.81) $p = 0.15$	6 centers, Toronto, Ontario, Canada
9	32,661,006	A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe SARS-CoV-2 [15]	81	(a) Interferon β-1a + hydroxychloroquine + lopinavir-ritonavir OR atazanavir-ritonavir (b) Treatment a except interferon-β-1b	Severe SARS-CoV-2	Time from starting the interventions to the clinical response No significant difference IFN group: 9.74 ± 5.8 Control group: 8.39 ± 4.9 Hazard ratio [HR], 1.10; 95% CI, 0.64 to 1.87 $p = 0.72$	1 center, Tehran, Tehran Province, Iran

Table 2 continued

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
10	33,189,161	Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial [16]	101	(a) Interferon beta-1a (b) Placebo	Mild-severe SARS-CoV-2	Change in clinical condition on the WHO Ordinal Scale for Clinical Improvement Day 15/16 odds ratio 2.32 [95% CI 1.07–5.04] $p = 0.033$ Day 28 odds ratio: 3.15 [1.39–7.14] $p = 0.006$ Odds of improvement were greater in the IFN group than in the placebo group	20 centers; Hull, England; Cottingham, England; Birmingham, England; Leicester, England; Oxford, England; Manchester, England; Nottingham, England; Bradford, England; Belfast, Northern Ireland, Southampton, England; Salisbury, England; Maidenhead, England

Table 2 continued

	PMID	Title	Total study sample	Treatment arms	Stage of treatment administration	Primary outcomes	Location
11	33,275,267	The dual role of anti-viral therapy in the treatment of Coronavirus disease 2019	148	(a) Standard care (supplemental oxygen, ventilation, antibiotics) (b) Interferon-alpha-2b (c) Interferon-alpha-2b + lopinavir/ritonavir	Mild-severe SARS-CoV-2	Average time to two consecutive negative RT-PCR tests (viral clearance rate) Standard care, 14 days; IFN alfa-2b, 15.5 days; and IFN alfa-2b combined with lopinavir plus ritonavir 17.5 days Results suggest that early treatment with IFN alfa-2b/ later treatment with IFN alfa- 2b combined with lopinavir plus ritonavir may help fight SARS-CoV-2, but overall minimal effect of IFN administration	1 center, Beijing, China

multiple sclerosis [17]. Studies that chose to use IFN-β as an intervention acknowledged that the intervention was less common when treating viral infections, but showed promise in retrospective and case series analyses, as well as in clinical trials, particularly RCTs. By contrast, IFN-α is the IFN class typically used to treat viral infections, such as hepatitis C, hepatitis B and human herpes [17]. The studies that used IFN-α reasoned that clinical efficacy was demonstrated in previous viral respiratory infections, including SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The last classification of IFN studied was IFN-λ. This interferon is produced by T-cell lymphocytes and is a type III interferon, but is less prevalent in the body [17]. The receptor complex for IFN-λ is expressed on a few cells, such as the epithelial cells in the respiratory tract. The specificity of IFN-λ to the respiratory tract was a rationale behind the studies exploring IFN-λ, as were mice models demonstrating lower mortality and influenza viral loads during IFN-λ treatment post-infection compared to mice treated with IFN-α [12, 18]. Details regarding the types of interferons and subclasses are provided in Table 3.

Dosage of IFN administered to study participants varied greatly across studies as well, from 0.50 μg daily to a single 180 μg dose to a total of 264 μg. In the study using a single 180 μg subcutaneous injection of IFN-γ, the investigators noted that in vitro success with IFN and SARS-CoV-2 was not replicated in human studies, an issue that may be due to dosage discrepancies [19]. Specifically, the study concluded that in an average 70 kg adult, 180 μg Lambda would result in 2.60 μg/kg/dose, which was 1/3 of the dose given to mice, potentially rendering the dose less effective [12]. By contrast, a study protocol for IFNβ-1a recommended subcutaneous injections totaling 264 mcg (72 million IUs) over 2 weeks, which is far higher than many of the dosages administered in the other clinical trials reviewed in this study [20].

Late Intervention Versus Early Intervention of IFN Therapy

Finally, the timing of intervention varied considerably across studies. Some studies suggest that early administration of IFN is more effective in reducing disease severity and mortality due to SARS-CoV-2 compared to late administration [15, 21]. IFN therapy has been theorized to accelerate viral clearance if administered to early stage patients, subsequently leading to earlier recovery or reduction of severe illness [8]. Additionally, it is hypothesized that early-stage treatment may be associated with a reduction in virus transmission [22]. Despite this, the majority of studies in this review examined the efficacy of IFN as a treatment for severe SARS-COV-2, particularly with inpatient participants. The reported median days between symptom onset and randomization or treatment administration ranged from 3 to 14 days, while only 4 of the 11 studies administered IFN within 5 days or less of symptom onset. Three of these four studies concluded that IFN therapy was effective in reducing symptoms of SARS-CoV-2, while the remaining studies primarily reported no significant difference or worse outcomes upon administration of IFN.

DISCUSSION

Potential for Interferons as Therapeutics for SARS-CoV-2

Interferons hold potential for use as treatment for SARS-CoV-2. They are easy to administer, provider-initiated and have the potential to increase the rate of viral clearance and decrease time to clinical improvement, especially when administered during early-onset of SARS-CoV-2. Furthermore, the reported side effects of interferon treatment are minimal (e.g., nausea, temporary digestion issues). However, the most effective use of interferon, according to the reviewed studies, is in combination with other repurposed antiretroviral drugs—most commonly lopinavir, ritonavir and remdesivir. These medications are typically more accessible than interferon treatment, as oral

Table 3 Details about interferons, including types, subtypes, molecular mechanisms, SARS-CoV-2 related properties, therapy names, phases of testing and patent ownership

Type and molecular mechanism of action	Subtype	Generic names	Trade names	Phase (preclinical, phase 1/2/3/4)	Patent ownership
IFN-α (type 1)	IFN-α1	Interferon alfa-1	N/A	Preclinical	Novagen Holding Corp
	IFN-α2a	Interferon alfa-2a Peginterferon alfa-2a	Roferon®-A (interferon alfa-2a), Pegasys	Phase 3	Hoffmann La Roche
	IFN-α2b	alpha interferon, IFN-alpha	Intron® A (interferon alfa-2b)	Phase 4	Intron A: Biogen/ Schering-Plough
	IFN-α4	N/A	N/A	Preclinical	AIM Immunotech Inc
	IFN-α5	N/A	NAHE 001	Phase 2	Digna Biotech
	IFN-α6	N/A	N/A	Preclinical	N/A
	IFN-α7	N/A	N/A	Preclinical	AIM Immunotech Inc
Rapid induction of antibody response, stimulated by virus and produced by both immune and non-immune cells, primarily induces viral resistance. Mostly involved in innate immunity to alert the organism of viral infection by detection of double stranded DNA and inhibit virus multiplication	IFN-α8	N/A	PF-04849285, rhIFN-α8	Preclinical	Imperial College of Science Technology and Medicine, AIM Immunotech Inc
	IFN-α10	Interferon alfa-10	IFN-alpha C	Preclinical	AIM Immunotech Inc
	IFN-α13	Interferon alpha-13	N/A	Preclinical	N/A
	IFN-α14	rhIFN-α14	N/A	Preclinical	Imperial College of Science Technology and Medicine
	IFN-α16	N/A	N/A	Preclinical	AIM Immunotech Inc
	IFN-α17	N/A	N/A	Preclinical	AIM Immunotech Inc
	IFN-α21	N/A	N/A	Preclinical	AIM Immunotech Inc
	Multi-subtype	IFN-alpha	Multiferon	Phase 4	Viragen

Table 3 continued

Type and molecular mechanism of action	Subtype	Generic names	Trade names	Phase (preclinical, phase 1/2/3/4)	Patent ownership
IFN-β (type 1)	IFN-β1a	N/A	Avonex®, Plegridy®, Rebif®	Phase 4	Biogen Inc, EMD Serono Canada Inc
Expressed by all nucleated cells and may be expressed in isolation of most type 1 IFNs. Primary function is to induce viral resistance in cells	IFN-β1b	N/A	BETASERON®, Extavia®		Bayer Inc, Novartis Pharmaceuticals Canada Inc
IFN-K (type 1)	N/A	Interferon-α kinoid	N/A	Phase 3	Neovacs
Primarily expressed by keratinocytes and has a role against herpes simplex virus, papilloma virus, and cutaneous lupus erythematosus. Constitutively expressed, but exhibits low anti-viral activity					
IFN-δ (type 1)	N/A	N/A	N/A	N/A	N/A
Antiviral and immunomodulatory activity					
IFN-E (type 1):	N/A	IFN-epsilon	N/A	N/A	Elf Sanofi SA, Abbott Biotech Inc, Repligen Corp
Constitutively expressed, functions like type 1 interferons					

Table 3 continued

Type and molecular mechanism of action	Subtype	Generic names	Trade names	Phase (preclinical, phase 1/2/3/4)	Patent ownership
IFN-ω (type 1) Secreted by visus-infected leukocytes, suggested to neutralize autoantibodies in human disease, including with SARS-CoV-2	N/A	IFN-omega	rFeIFN-ω, Virbagen Omega	Preclinical	Общество с ограниченной ответственностью "Научно-Технологический Центр "БиоИнвест" (rFeIFN-ω), Virbac SA (Virbagen)
IFN-τ (type 1) Promotes anti-viral activity and suppresses viral replication	N/A	IFN-tau	N/A	N/A	N/A
IFN-ζ (type 1) Displays antiviral, immunomodulatory, and antitumor effects	N/A	IFN-zeta/ limitin	N/A	N/A	N/A
IFN-i (type 1)	N/A	N/A	N/A	N/A	N/A
IFN-γ (type II) Primary activator of macrophages, stimulates natural killer cells and neutrophils, up-regulation of pathogen recognition and anti-viral activities	N/A	Interferon gamma-1b	Immukin, Actimmune®	Phase 2,3 RCTs	Horizon Therapeutics PLC (generic), Boehringer Ingelheim (Immukin), Horizon Therapeutics Ireland Dac (Actimmune)

Table 3 continued

Type and molecular mechanism of action	Subtype	Generic names	Trade names	Phase (preclinical, phase 1/2/3/4)	Patent ownership
IFN-λ	IFN-λ3 (type III): IFN-λ hampers lung repair by inducing p53 and inhibiting epithelial proliferation and differentiation	N/A	Pegylated type 3 interferon	Preclinical	Zymogenetics LLC, Squibb Bristol Myers Co, Hausman Diana F, Dodds Micahel G
Activated by viral infections, triggers antiviral activity not limited to specific cell types, unlike type 1 IFNs. Provides weaker direct antiviral protection but strong antiviral immunity	IFN-λ1 (type III): Activity in innate antiviral responses, particularly against respiratory pathogens	N/A	Peginterferon Lambda-1a	Phase 4	Nanogen Pharmaceutical Biotechnology, Zymogenetics LLC, Squibb Bristol Myers Co, Hausman Diana F, Dodds Micahel G
	IFN-λ2: Alleviates/reduces viral respiratory disorders, such as asthma arising from rhinovirus infection	N/A	Pegylated type 3 interferon	Preclinical	Zymogenetics LLC, Squibb Bristol Myers Co, Hausman Diana F, Dodds Micahel G

administration is offered through a variety of brands worldwide. By contrast, interferons are typically used to treat very specific viral infections, including chronic hepatitis, multiple sclerosis and leukemias [23].

Despite the potential accessibility concerns with interferons, the literature suggests that administration within 5–6 days of symptom onset/diagnosis may improve outcomes in patients with SARS-CoV-2, particularly time to viral clearance and time to clinical improvement. Additionally, while only 5 of the 11 reviewed studies found significant differences between interferon and control groups, the studies that administered interferon during early onset of SARS-CoV-2 symptoms had clinically significant improved outcomes in mortality, time to clinical improvement/recovery and time to viral clearance. As such, it can be concluded that interferon therapy in combination with additional antiretroviral treatment has potential to be an effective treatment for early-onset SARS-CoV-2.

However, the variability in study methods and IFN-related outcomes was too disparate to enable comparability between studies and summarize the efficacy of IFN as a treatment for SARS-CoV-2. In addition to consistent study indicators to evaluate effectiveness, data must also be collected on cost, accessibility, drug

interactions and distribution of IFN, as available data are currently extremely limited. Consequently, it is recommended that in addition to RCTs on IFN therapy, implementation research should be conducted to allow practitioners to make an informed decision on the use of IFN for SARS-CoV-2 treatment.

Recommendations

1. Standardized Outcome Measures. A major challenge in understanding whether interferon therapies have potential use for SARS-CoV-2 is the lack of comparable outcome measures between studies. While recommendations have been made for core indicators to collect for SARS-CoV-2 (e.g., 2019 Core Indicator set) [24], we recommend potential therapeutics also follow a core set of indicators. For IFNs, potential indicators could include: time to viral clearance (defined as two negative RT-PCR tests), time to clinical improvement using a standardized ordinal scale, and mortality at day 28 among hospitalized patients. This would allow us to capture outcomes at varying stages of prevention and disease progression but most importantly would allow for comparability across studies and contexts to facilitate evidence generation and synthesis.

2. Dedicated Analyses by Interferon Type. The studies included in our review employed a variety of types of IFNs as interventions, and current data on the effectiveness of IFN treatment are based on the results of each type of IFN. Additionally, most of the studies indicated that there was a lack of clinical trial data on any type of IFN as an intervention, leading them to use ongoing trials to reason their choice of IFN intervention. These ongoing studies were generally small, with several recruiting < 50 participants in each arm. As such, the generalizability of the results is uncertain, and current data are insufficient to identify a primary form of IFN as a treatment option for SARS-CoV-2. It is also worth noting that patients with critical symptomatic SARS-CoV-2 infections have been found to have circulating autoantibodies that may neutralize IFN-α and IFN-β, especially in populations over the age of 80 [25, 26]. Larger trials should be conducted with each type of IFN therapy to identify the efficacy of each approach.

3. Analyses of Effectiveness by Disease Stage. The studies included in our review examined the impact of IFN treatment at different stages of SARS-CoV-2 infection. Future studies should aim to identify the impacts of IFN at each stage of infection, as there is currently little to no support for IFN therapy as a treatment for severe SARS-CoV-2. Additionally, inpatient populations may not necessarily correspond with disease severity, and studies should use standardized indicators (e.g., the clinical spectrum of SARS-CoV-2 infection established by the National Institute of Health [27]) to quantify disease severity despite participants' hospitalization status.

4. Exploration of Higher IFN Dosage. Despite the well-tolerated effects of IFN therapy, only 6 out of the 11 studies in our review administered an IFN dosage of the recommended amount or higher. This suggests that additional clinical trials should be done with increased dosage amounts and increased frequency to examine the full potential of IFN therapy against SARS-CoV-2.

5. Cost Analysis. The cost of IFN, adherence and accessibility must be considered in scaling up IFN therapy to treat SARS-CoV-2. In Vietnam and Brazil, the weekly cost to treat hepatitis C virus (HCV) with IFN therapy ranged from $25.32 to $109.07 USD, depending on the subtype of interferon used [28, 29]. While IFN therapy regimens for SARS-COV-2 are shorter (4 weeks compared to 24–48 weeks), cost may remain a barrier to scale-up [29]. IFN therapy is most effective during the early stages of SARS-CoV-2 infection, which may further reduce costs associated with long recovery times. The potential to provide IFN therapy in combination with antivirals is promising, but considerations must be made for antiviral adherence. Poor adherence could lengthen recovery, increasing overall costs [30]. Fortunately, IFN therapy can be offered on alternate days, weekly or biweekly, a schedule that may reduce the burden on patients and improve adherence.

CONCLUSION

Exploring therapies for SARS-CoV-2 is relevant and urgent, especially considering the inequitable access to SARS-CoV-2 vaccines, with some countries reporting < 30% of their population vaccinated [31]. IFN therapies' unique administration schedule (e.g., can be administered once, weekly or more in severe cases), limited adverse effects and minimal follow-up [2] make IFN a compelling treatment option in populations with fewer or lower-skilled providers and limited access to pharmaceuticals. However, the lack of comparable outcome measures and high variability of intervention types and administration impede evidence synthesis. Standardized outcomes and reporting for interferon studies are urgently needed to facilitate evidence synthesis and generation before patients will be able to benefit from IFN's therapeutic use.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study design. Material preparation, data collection and analysis were performed by Diya Jhuti and Dr Angeli Rawat. The first draft of the manuscript was written by Diya Jhuti and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosures. Diya Jhuti, Angeli Rawat, Christina M Guo, Lindsay A Wilson, Edward J Mills and Jamie I Forrest all have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies involving human participants or animals performed by any of the authors.

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