Type I Interferon

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Together with type III IFNs, Type I Interferons (IFNs-I) represent the first line of immune defense against viral infections. In the case of RNA viruses, after recognition of viral products by pattern recognition receptors (PRRs), such as the main cytosolic receptors RNA helicases retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5), the signal converges on the activation of the mitochondrial antiviral signaling protein (MAVS), that, in turns, activates the TANK-binding kinase 1 (TBK1), leading to the phosphorylation and activation of IFN-regulatory factors 3 and 7 (IRF3, IRF7) [6,7]. IRFs then translocate to the nucleus and induce the production of IFNs-I (IFNα, IFNβ, IFNε, IFNτ, IFNκ, IFNω, IFNδ and IFNζ).

type I IFNs innate immunity SARS-CoV-2 COVID-19

1. Introduction

In December 2019, an outbreak of acute respiratory syndrome of unknown etiology was reported in Wuhan, China [1]. Soon thereafter, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of coronavirus infectious disease 2019 (COVID-19) and, in March 2020, the World Health Organization declared the COVID-19 outbreak a global pandemic [1][2]. As of 13 July 2021, the pandemic has accounted for over 210 million confirmed cases of COVID-19 worldwide, including more than 4 million deaths [3], together with an enormous social and economic impact throughout the world [4]. SARS-CoV-2 infection manifests with a broad spectrum of clinical patterns, resulting in asymptomatic cases in most individuals and inducing mild to severe illness in others, with fever, cough, headache and myalgia identified as common symptoms in moderate COVID-19, whereas severe pneumonia requiring intensive care unit and mechanical ventilation occurs in critically ill patients [5].

Production and secretion of IFN into the surrounding tissue results in the binding of IFNs to their receptor (IFNAR) in an autocrine and paracrine manner. The interaction with IFNAR activates the receptor-associated protein tyrosine kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2), which in turn phosphorylate signal transducer and activator of transcription 1 and 2 (STAT1 and STAT2) molecules, leading to their dimerization, nuclear translocation and binding to IRF9 to form the ISG factor 3 (ISGF3) complex. These events culminate with the transcription of hundreds of interferon stimulated genes (ISGs), that inhibit virus multiplication at distinct levels, potentiate the innate antiviral immunity and stimulate an adaptive response [6].

Many, if not all viruses, including the human coronaviruses SARS-CoV and MERS-CoV [7][8], have evolved distinct mechanisms to escape immune surveillance, including strategies to avoid PRRs recognition and the expression of

viral proteins that impair IFN signaling at different levels [8][9]. Therefore, with the experience gained during the previous Betacoronavirus outbreaks [7], the IFN response in SARS-CoV-2 infection was promptly investigated.

2. IFN-Based Therapy for COVID-19

Given the urgent need for an effective treatment for patients suffering from COVID-19, the number of registered clinical trials increased significantly in the past year; most studies were primarily designed to evaluate the efficacy and safety of treatment with compounds already approved for clinical use. The dysregulation of type I IFN response commonly observed during coronaviruses infection [7][10][11] and the high sensitivity of SARS-CoV-2 to IFN-I identified through in vitro experiments [12][13] raised interest in strategies based on these cytokines. Further indications in favor of the clinical use are provided by the encouraging results obtained from the treatment of diseases etiologically linked (or not) to viral infection (reviewed in [14]).

Several clinical trials have been conducted and are still ongoing to examine the potential use of different IFN-I subtypes and routes of administration for improving the clinical outcome of patients infected with the new coronavirus (**Table 1**).

Table 1. IFN-based treatment studies.

Authors	IFN Therapy	IFN Administration	Type of Study	N. Patients	Disease Stage	Outcome (Intervention vs. Control)
Hung, I.F.-N. et al. [15]	IFN-β-1b 5 days from symptoms onset	Subcutaneous	Multicentre prospective open-label randomized phase 2 Trial	86 intervention group 41 control group	Hospitalized	Hospitalization: 9 vs. 14.5 days Mortality: 0% vs. 0% Serious adverse effects: 0% vs. 2%
Malhani, A.A. et al. [16]	IFN-β-1b 4 days from symptoms onset	Subcutaneous	Observational study IFN-based vs. FPV treatment	68 treated with IFN 154 treated with FPV	Mild–moderate–severe	Mortality: 9% vs. 12% Need of systemic corticosteroids: 57% vs. 77%
Davoudi-Monfared, E. et al. [17]	IFN-β-1a 10 days from symptoms onset	Subcutaneous	Open-label randomized clinical trial	42 intervention group 39 control group	Severe	Hospitalization: 14.8 vs. 12.2 days Mortality: 19% vs. 43.6% Serious adverse effects: no differences between groups
Dastan, F. et al. [18]	IFN-β-1a 6.5 days	Subcutaneous	Prospective non-	20 intervention	Severe	Hospitalization: 16.8 days

Authors	IFN Therapy	IFN Administration	Type of Study	N. Patients	Disease Stage	Outcome (Intervention vs. Control)
	from symptoms onset		controlled trial	group only		Mortality: 0% Serious adverse effects: 0%
Ader, F. et al. [19]	IFN-β-1a 10 days from symptoms onset	Subcutaneous	Open-label randomized adaptive clinical trial	145 intervention group 148 control group	Moderate–severe	Hospital discharge at day 29 significantly higher than control arm
Meng, Z. et al. [20]	Recombinant human (rh) IFN-α Preventive Therapeutic Strategy	Intranasal	Prospective, open-label study	2944 intervention group only	None	28-day incidence of COVID-19/new-onset clinical symptoms: 0% Serious adverse effects: 0%
Zhou, Q. et al. [21]	IFN-α2b 8 days from symptoms onset	Inhaled	Uncontrolled, exploratory study	53 intervention group 24 control group	Moderate	Accelerated viral clearance/reduction in systemic inflammation markers (circulating IL-6 and CRP levels)
Monk, P.D. et al. [22]	IFN-β-1a 24 h from SARS-CoV-2 positive test	Inhaled	Randomized, double-blind, placebo-controlled, phase 2 pilot trial	50 intervention group 51 control group	Moderate–severe	Greater odds of improvement in OSCI scale for intervention group Mortality: 0% vs. 6% Serious adverse effects: 15% vs. 28%

IFN, Interferon; rhIFN-α, Recombinant human IFN-α; IL-6, Interleukin 6; CRP, C-reactive protein; OSCI, Ordinal Scale for Clinical Improvement.

...ent with ...avir and ...eviation, ...sides, no significant adverse events were reported [15]. In addition, the combination IFN-β1b plus lopinavir/ritonavir and ribavirin was investigated in a single center observational study showing lower 28-day mortality (9% vs. 12%) and less need for systemic corticosteroids, as compared to favipiravir (FPV)-treated individuals in a cohort of hospitalized patients with non-critical COVID-19 [16].

Previously reported as a candidate agent for the treatment of SARS-CoV infection [23], IFN-β1a administration was also investigated in a similar setting including lopinavir-ritonavir or atazanavir-ritonavir plus hydroxychloroquine in COVID-19 cases. In this randomized clinical trial of 81 patients, the subcutaneous administration of IFN-β1a in severely ill patients resulted in significantly lower 28-day mortality and increased discharge rate on day 14. Interestingly, analysis based on the time of treatment initiation showed greater efficacy in mortality reduction when IFN was administered early during the disease evolution [17]. The importance of administration timing has been highlighted by a recent report in which delayed IFN-β administration in MERS-CoV-infected mice exacerbated a pro-inflammatory state and increased infiltration of activated monocytes, macrophages and neutrophils in the lung, ultimately resulting in a worse outcome (e.g., fatal pneumonia), compared to mice treated within one day after

infection [24]. Thus, the IFNs response timing relative to the virus replication seems to be a critical factor that may profoundly affect the disease course. Although obtained on a small number of patients (*n* = 20), further data support the use of IFN-β1a, hydroxychloroquine and lopinavir/ritonavir for the management of COVID-19 [18]. Conversely, in the DisCoVeRy phase III trial (NCT 04315948) the lopinavir/ritonavir plus IFN-β1a arm (145 adults hospitalized for COVID-19) did not show clinical improvement at day 15 nor viral clearance in respiratory tract specimens, while hospital discharge at day 29 was significantly higher than the control arm (HR, 0.72; 95% CI, 0.54–0.96; $p = 0.026$) [19].

In order to reach an adequate concentration in the upper and lower respiratory tracts and limit systemic exposure to IFN, other routes of administration were also evaluated. Nasal drops of recombinant human IFN-α provided a valuable prophylactic measure in individuals at high risk of infection. An experimental trial of 2944 healthcare workers in Hubei (China), compared to new-onset COVID-19 in healthcare workers in the same Province (including Wuhan), showed that the 28-day incidence of COVID-19 and the incidence of new-onset clinical symptoms with negative images for pneumonia, were zero in the treated group [20]. Furthermore, treatment with nebulized IFN-α2b, with or without Umifenovir (Arbidol), was tested on 53 of 77 confirmed COVID-19 patients. In this exploratory study, Zhou et al. [21] reported a significant reduction in the duration of detectable SARS-CoV-2 RNA in the upper respiratory tract concurrently with reduced duration of high IL-6 and C-reactive protein circulating levels [21]. Another promising approach via nebulization involves the use of IFN-β1a (SNG001). Results from a phase II trial, marked by a strong odds reduction (79%) of developing severe disease or dying in SNG001-treated patients than in the placebo group [22], have recently led to recruitment for a randomized, double-blind, placebo-controlled, phase III trial to determine the efficacy and safety for the treatment of hospitalized patients who require oxygen supplementation (ClinicalTrials.gov: NCT04732949).

3. Conclusions

During the past year, it has become clear that an enormous heterogeneity exists in the magnitude and kinetics of the early innate immune response during SARS-CoV-2 infection, suggesting that a dysregulated and/or delayed IFN response are likely associated with a poor prognosis. An accurate disease status definition, the consideration of inherent genetic defects and comorbidities that could affect the IFN response against viral infection may provide new insights and foster a better understanding of IFN response during SARS-CoV-2 infection.

Recent genetic observations also highlight the association between severe COVID-19 outcomes, rare genetic variants and/or presence of auto-Abs, both impairing type I IFNs signaling. This scenario could have important clinical implications; detection of genetic defects or auto- Abs in SARS-CoV-2 infected patients could be used as a prognostic factor of severe disease; also, these patients could undergo personalized therapy to decrease the concentration of anti- type I IFNs auto-Abs, as already demonstrated in four patients [25]; finally, an IFN-based therapy could be considered. Nevertheless, while beneficial in the early phase of infection when the antiviral activity of IFNs limited SARS-CoV-2 replication, a detrimental response may be elicited in late stages, when uncontrolled IFN response could drive inflammatory lung pathology.

The encouraging findings obtained to date from ongoing clinical trials indicate that administration of type I IFN may represent a valuable strategy to combat COVID-19 at early stages of disease. Further investigations are necessary to develop targeted therapies according to the disease severity, bearing in mind the importance of the innate response as a first-line immune defense against viral infection.

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