Journal of Clinical Immunology
https://doi.org/10.1007/s10875-021-01068-6

COMMENTARY

Harnessing Type I IFN Immunity Against SARS-CoV-2 with Early Administration of IFN-β

Donald C. Vinh[1] · Laurent Abel[2,3,4] · Paul Bastard[2,3,4] · Matthew P. Cheng[1] · Antonio Condino-Neto[5] · Peter K. Gregersen[6] · Filomeen Haerynck[7] · Maria-Pia Cicalese[8] · David Hagin[9] · Pere Soler-Palacín[10] · Anna M. Planas[11] · Aurora Pujol[12,13] · Luigi D. Notarangelo[14] · Qian Zhang[2] · Helen C. Su[14] · Jean-Laurent Casanova[2,3,4,15] · Isabelle Meyts[16,17] · On behalf of the COVID Human Genetic Effort

Received: 26 March 2021 / Accepted: 17 May 2021

Introduction

Since December 2019, over 150 million individuals have been infected with SARS-CoV-2 globally. While most cases (>95%) are asymptomatic or mild, a small proportion develop moderate, severe, or critical COVID-19 pneumonia requiring hospitalization, at times in the intensive care unit [1]. At least 2 million patients have already died [2]. The main epidemiological risk factor associated with critical pneumonia or death is age > 65 years; however, life-threatening COVID-19 has also affected younger people, albeit sporadically. Studies have suggested that type I interferon (IFN) immunity contributes to the control of SARS-CoV-2 infection [3–8]. Notably, inborn errors of TLR3- and IRF7-dependent type I IFN production or amplification underlie severe disease in ~3% of a cohort of relatively young adult patients analyzed by the COVID Human Genetic Effort (COVIDhge.com) [3]. In at least an additional 10% of cases, high levels of pre-existing auto-antibodies (auto-Abs) neutralizing most type I IFNs, but rarely IFN-β, abrogate type I IFN–dependent control of SARS-CoV-2 replication in vitro, thereby underlying critical disease in vivo [3, 4, 9, 10]. This observation was replicated in other cohorts [11–15]. The mean age of patients with inborn errors was 48 years, while that of patients with auto-Abs was 65 years. These findings support a two-step model of COVID-19 pathogenesis: defective type I IFN immunity in the first

✉ Isabelle Meyts
isabelle.meyts@uzleuven.be

[1] McGill University Health Centre, Montreal, Canada

[2] St Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY 10065, USA

[3] Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM UMR 1163, Necker Hospital for Sick Children, 75015 Paris, France

[4] University of Paris, Imagine Institute, 75015 Paris, France

[5] University of São Paulo, São Paulo, Brazil

[6] Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA

[7] Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPIG), PID Research Lab, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent University, Ghent, Belgium

[8] Pediatric Immunohematology and Bone Marrow Transplantation Unit, San Raffaele Telethon Institute for Gene Therapy (SR-Tiget), IRCCS San Raffaele Scientific Institute, Milan, Italy

[9] Allergy and Clinical Immunology Unit, Department of Medicine, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv, Israel

[10] Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain

[11] IIBB-CSIC, IDIBAPS, Barcelona, Catalonia, Spain

[12] Neurometabolic Diseases Laboratory, IDIBELL–Hospital Duran I Reynals; Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Catalonia, Spain

[13] CIBERER U759, ISCiii, Madrid, Spain

[14] Laboratory of Clinical Immunology and Microbiology, National Institutes of Health, Bethesda, MD, USA

[15] Howard Hughes Medical Institute, New York, NY, USA

[16] Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

[17] Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium

Published online: 08 June 2021

hours and days of infection leads to uncontrolled viral replication with spread to the lungs and other tissues, with subsequent excessive leukocyte recruitment, underlying uncontrolled inflammation [5]. This model of early deficient type I IFN function provides a framework for novel preventive and therapeutic approaches of COVID-19. Here, we explore two therapeutic routes that aim to restore protective type I IFN immunity: [1] the early administration of IFN-β in ambulatory subjects, including exposed individuals prior to infection, pre-symptomatic infected individuals and symptomatic individuals, and [2] the removal of auto-Abs to type I IFN in hospitalized patients. We also discuss the implications of these findings for other preventive and therapeutic interventions, including B cell depletion, JAK inhibitors, intravenous immunoglobulins, the use of convalescent plasma and virus-specific mAbs, and vaccination. This discussion is timely, as more than one year into the pandemic, we are still in the dark about the best prevention and treatment for severe COVID-19 pneumonia, while the emergence of more contagious viral variants, causing more severe disease, raises concerns regarding the efficacy of the nascent vaccination programs [16, 17].

Vaccines for COVID-19: Where Do We Stand?

Currently, several COVID-19 vaccines are in use, and numerous others are in different phases of development. Despite their excellent efficacy and safety profile, the finding that sera from vaccinated individuals showed reduced in vitro neutralization of 5 of 10 pseudoviruses representing circulating SARS-CoV-2 strains is concerning [18]. Moreover, protection from vaccines may wane and not all people will be able to tolerate the vaccines or mount protective responses. For instance, a word of caution is needed for the use of mRNA vaccines in patients with interferonopathies (i.e., autoinflammatory conditions due to excessive type I IFN activity), as these vaccines may potentially induce exaggerated type I IFN responses, despite the introduction of pseudouridine instead of uridine to reduce recognition by nucleic acid sensors. Overall, surveillance studies documenting both safety and efficacy are critically needed in patients with inborn errors of immunity and their phenocopies. Germane to the COVIDhge findings of deficient type I IFN activity in severe COVID-19, more specific questions arise. First, is vaccine efficiency maintained in patients with a genetic or auto-immune phenocopy of type I IFN defect? Indeed, type I IFN has been described to enhance antibody responses and isotype switching by effects on dendritic cells [19]. Do the current vaccines induce sufficient adaptive immunity to compensate for a patient's innate defect in type I IFN or for the pre-existing anti-type I IFN auto-Abs? Is the clinical effectiveness of the vaccines comparable between those with genetic defects of type I IFN response pathway and those with auto-Abs versus the general population? Although reports from patients with genetic type I IFN defects have not raised concerns about impaired vaccine responses, longitudinal data will be required to more definitively address these questions [20, 21]. The COVIDhge data also open new considerations on safety. As some type I IFN pathway defects, especially autosomal recessive (AR) deficiency of STAT2, IFNAR1, and IFNAR2, predispose to severe disease with live attenuated vaccine (LAV), and as anti-type I IFN auto-Abs can underlie disease caused by the yellow fever vaccine, special caution will be needed with SARS-CoV-2 vaccine strategies that use LAV [22]. We must also recognize that, as SARS-CoV-2 variants with potential to escape vaccine coverage emerge, it is possible that individuals with monogenic or auto-Ab-mediated impairment of type I IFN responses continue to remain at risk for severe disease, despite vaccination. The corollary would propose that individuals who develop COVID-19 disease following vaccination, and perhaps those who are repeatedly re-infected as well, may harbor known or novel inborn errors of immunity.

Convalescent Plasma and mAbs

Convalescent plasma (CP) from recovered patients is being administered in severe and critical COVID-19, prompted by historical experience with SARS-CoV, MERS-CoV, and 1918 Spanish flu [23, 24]. The rationale is that passive immunization against SARS-CoV-2 can ameliorate disease by decreasing virus spread and replication. It is expected to be beneficial mainly in the initial phases of disease. Risks of CP therapy include those of standard plasma infusions; for instance, volume overload and transfusion-related acute lung injury require special care [23, 25]. A theoretical risk is antibody-dependent enhancement, in which non-neutralizing antibodies against SARS-CoV-2 worsen disease by engaging Fc receptors which modulate effector functions of monocytes/macrophages and mediate cytokine release [26]. Eight randomized clinical trials (RCTs) using CP have been reported and most failed to show a beneficial effect on clinical status or mortality, conflicting with the observational studies [27–29]. Subsequently, an additional double-blind placebo-controlled clinical trial showed no efficacy in improving morbidity/mortality in patients with severe COVID-19 when administered at a median of 8 days after symptom onset, whereas another double-blind placebo-controlled clinical trial showed decreased disease progression in mildly affected patients when administered within 72 h after symptom onset [30, 31]. There are over 100 ongoing studies evaluating CP. These studies need to teach us [1] the minimum levels of anti-SARS-CoV-2 neutralizing antibodies needed to prevent or abort development of severe disease; [2] the optimal timing of plasma collection from donors after disease resolution; and

[3] the optimal dosing and timing of infusions relative to symptom onset in recipients [32, 33].

In the context of the findings of the COVIDhge, the main concern is that CP, if harvested from severely ill or hospitalized COVID-19 patients, may contain neutralizing type I IFN auto-Abs [15]. In that case, CP therapy could worsen disease in the recipient. Thus, CP should only be collected from asymptomatic or mildly ill COVID-19 patients and must be tested for neutralizing auto-Abs against type I IFN, even though at present, the threshold of auto-Abs that leads to critical COVID-19 has yet to be defined. Of note, the general application of such strategy is only possible when and where a standardized, validated assay to detect neutralizing anti-type I IFN auto-Abs is readily available with a quick turnaround time (<24 h). Recombinant monoclonal antibodies, targeted against SARS-CoV-2 spike protein, obviate these concerns and are potentially safer [34–36]. Moreover, the neutralizing titers achieved with for instance REGN-COV2 (a cocktail of casirivimab plus imdevimab, two non-competing neutralizing human IgG1 antibodies targeting the receptor binding domain of the spike protein) were more than 1000 times the titers achievable with CP. A combination of bamlanivimab and etesevimab (two other non-competing anti-spike neutralizing monoclonal antibodies derived from 2 patients who recovered from COVID-19), but not bamlanivimab alone, administered within 72 h of onset, reduced viral load and resulted in a decreased hospitalization rate compared with placebo in mild-to-moderate COVID-19 [36]. REGN-COV2 had a profound and rapid effect on viral load, with most reduction occurring within 48 h and with a stronger effect in individuals with a high viral load [35]. Studies of the impact on clinical outcome as a primary outcome are ongoing. However, viral strains carrying mutations in the target epitopes of SARS-CoV-2 spike protein have already been described, clouding the future of monoclonal antibody treatment [37].

Anti-inflammatory Drugs: Intravenous Immunoglobulin (IVIG), Corticosteroids, and Anti-IL6R Antagonists

In the two-step model of critical COVID-19, the first phase of insufficient type I IFN immunity results in deleterious pulmonary and systemic inflammation, calling for anti-inflammatory interventions. High-dose IVIG (0.8 g/kg to 2 g/kg) has immunomodulatory capacity, presumably via inhibition of complement system activation; decreased endothelial cell activation; anti-inflammatory effects on monocytes, macrophages, and neutrophils; and stimulation of regulatory T cells [38]. High-dose IVIG has been used in several studies in COVID-19 as an immunomodulatory therapy to treat multisystem inflammatory syndrome in children and adults associated with SARS-CoV-2 infection, but also in severe COVID-19 pneumonia [39–45]. A retrospective multicenter study conducted in China reported reduced mortality at day 28 in critically ill COVID-19 patients treated with high-dose IVIG [46]. Two RCTs with high-dose IVIG were recently published. The first study compared 1.2 g/kg IVIG plus hydroxychloroquine and lopinavir/ritonavir to the latter treatment alone, and its results did not support the use of IVIG [47]. A smaller study, with 30 patients in each treatment arm, showed a decreased mortality in patients with severe COVID-19 treated with IVIG [48]. More RCTs are needed to define efficacy, dosing, and timing of high-dose IVIG treatment. In light of COVIDhge findings, administration of high-dose IVIG might have the additional benefit of "washing out" the pathogenic anti-type I IFN auto-Abs [49]. High-dose IVIG are thus beneficial in immune thrombocytopenia [50] and Guillain-Barré syndrome [51]. Careful studies of the kinetics of anti-IFN-auto-Abs are necessary, together with longitudinal assessment of serum cytokines, to provide proof of principle for this approach.

Seven RCTs have examined the effect of low-dose steroids, as a broad-acting anti-inflammatory agent, in critical COVID-19, and one RCT in non-critical COVID-19. The largest trial, in 2104 subjects, showed a reduced 28-day mortality (22.9% vs. 25.7%) in dexamethasone versus usual care [52]. A meta-analysis of all trials showed a significant decrease in day 28 mortality for dexamethasone compared to supportive care in three trials, in patients with critical COVID-19 [53]. A more specific approach to dampen the cytokine storm in COVID-19 is by targeting IL-6, using the anti-IL6 receptor (IL6R) blocking monoclonal antibodies, tocilizumab, or sarilumab. Multiple observational studies hinted towards improved outcome using tocilizumab. Several RCTs have now been conducted in severe COVID-19 [54–60]. The largest trial, which focused on patients with critical COVID-19, reported reduced days on organ support and a small reduction mortality in patients receiving anti-IL6R antagonists versus placebo (27% in the pooled tocilizumab or sarilumab arm vs. 36% in the placebo arm, REMAP-CAP trial) [61]. Overall, the RCTs have been unimpressive in terms of beneficial effect on survival [62].

Anti-inflammatory Agents that Interfere with Type I IFNs: JAK Inhibitors

Several classes of drugs interfere with the type I IFN pathways, including antagonists/monoclonal antibodies targeting IFNAR/IFN. Janus kinase (JAK) inhibitors (Jakinibs) target many signaling pathways, depending on their selectivity [63]. Ruxolitinib inhibits JAK1 and JAK2 and thereby interferes with, respectively, the common cytokine receptor γ-chain (used by IL-2, IL-4, IL-7, IL-9, IL-15); the gp130 pathway (IL-6, IL-11, OSM, LIF); the class II cytokine receptor family (IFN-α/β, IFN-γ, IL-10) (JAK1); and the EPO, TPO, IFNγ,

and βc family (IL-3, IL-5, GM-CSF) (JAK2). Tofacitinib potently inhibits JAK3 next to JAK1 and thus may also impair the γc receptor family. Ruxolitinib is an especially potent inhibitor of type I IFN signaling. Finally, IFN-kinoid (IFN-α coupled to the carrier protein, keyhole limpet hemocyanin) induces the production of antibodies against all 13 IFNα [64]. These drugs are in various phases of development and clinical trials and some have been approved by the FDA to treat malignancies, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and systemic lupus erythematosus.

In the two-phase model of severe COVID-19, use of a Jakinib after the initial phase could dampen inflammatory cascades triggered by ligand-binding to the multiple cytokine receptors as described above. However, in the early phase, when type I IFN signaling is crucial for antiviral defense, the biological consequences of Jakinibs and IFN-kinoid resemble the phenotypes of patients with auto-Abs against type I IFNs [4] and AR IFNAR1 or IFNAR2 deficiency [3]. Thus, patients who are already receiving these agents, and become infected with SARS-CoV-2, are potentially at risk for severe COVID-19. Thus, it is prudent to consider halting of these drugs in the initial phase of SARS-CoV-2 infection. However, in a retrospective study, of three patients with Aicardi-Goutières syndrome on Jakinibs, 2 were asymptomatically infected and 1 only experienced a rash upon infection [65], although their excessive type I IFN signaling may be incompletely downregulated by the Jakinibs [65]. Additionally, Jakinibs have been or are being studied to treat patients with severe COVID-19 (e.g., ARDS; "cytokine release syndrome"). The ACTT-2 study demonstrated that the Jakinib baricitinib (in association with the antiviral remdesivir) reduced recovery time and accelerated improvement in clinical status in moderate-to-severe COVID-19 [66]. Remdesivir itself failed to show any beneficial effect on initiation of ventilation, duration of hospital stay, and mortality in the recent Interim WHO Solidarity Trial Report [16, 67]. One additional RCT using ruxolitinib versus placebo in hospitalized patients has recently been completed and 20 more are recruiting [68]. The finding of beneficial effects of Jakinibs in the second phase of moderate-to-severe COVID-19 disease is consistent with the two-stage disease model of COVID-19. However, as the threshold level of type I IFN activity and the duration of type I IFN activity required to mitigate COVID-19 are unknown, caution is required when using IFN-kinoid or Jakinibs.

B Cell and Plasmablast Depletion and BTK Inhibition: How About COVID?

Depletion of B cells can be achieved with an anti-CD20 antibody (e.g., rituximab). In mycobacterial infections due to anti-IFN-γ auto-antibodies, another phenocopy of an inborn error of immunity, rituximab has been used with success [69–73]. Depletion of plasmablasts can be achieved by antibodies targeting CD38 (e.g., daratumumab); the latter has been successfully used to treat multiple myeloma [74], autoimmune cytopenias [75], autoimmune organ diseases [76, 77], and infection due to auto-Abs to cytokines [78]. These depletive therapies have not been studied as acute treatment for COVID-19 in the context of RCT or, to our knowledge, even published as case reports. However, results of retrospective studies on the outcome of COVID-19 are inconclusive in patients previously on a B cell–depleting agent for underlying immune-mediated diseases, such as rheumatoid arthritis [79–83]. In the context of COVIDhge, B cell/plasmablast depletion can potentially be used to curb the ongoing secretion of neutralizing anti-type I IFN IgG. Of note, data from patients with X-linked agammaglobulinemia (XLA), which is caused by mutations in Bruton's tyrosine kinase (BTK), suggest they are not untowardly susceptible to severe COVID-19 [65, 84, 85]. This may suggest that absent development of protective neutralizing antibodies to COVID-19, as well as vaccination responses, may not predispose to severe COVID-19 [86]. An alternative or additional explanation may relate to reduced inflammatory cytokine release by BTK-deficient monocytes. In line with this are the promising results seen with the BTK inhibitors, acalabrutinib and ibrutinib, in patients infected with SARS-CoV-2 while on these drugs, and in an observational trial using acalabrutinib in hospitalized patients with severe COVID-19 [87, 88], in which the benefit correlated with the impairment of monocyte activation. Several clinical trials are under way to evaluate the potential benefit of BTK inhibitors in COVID-19. Whether such treatment is associated with persistent shedding of viable SARS-CoV-2 virus is unclear [89–92]. The question of prolonged shedding and temporary blunting of antibody responses will need to be studied when evaluating the use of B cell/plasmablast depletion during the management of COVID-19 in patients with auto-Abs. These patients may be at risk of re-infection and will not likely be able to respond to vaccines while the B cell deficiency persists.

Therapeutic Plasma Exchange (TPE): Past and Present

TPE refers to the removal of a large volume of plasma, typically 30–40 ml/kg, necessitating replacement of fluid by a colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution. In contrast, plasmapheresis (PP) is based on removing (not replacing) only 15% of plasma volume. TPE is currently used in over 60 medical conditions according to the American Society for Apheresis [93]. The rationale of TPE lies in the removal of a pathogenic substance from plasma, such as immune complexes, cryoglobulins, toxins, or lipids. More specifically, TPE has been used

successfully in conditions mediated by auto-antibodies, such as vasculitis, Guillain-Barré syndrome, Goodpasture syndrome, thrombotic thrombocytopenic purpura, and autoimmune hemolytic anemia, some of which are associated with viral infections [93]. TPE has also been applied in patients with shock-like presentation in the context of respiratory viral infection in an attempt to clear inflammatory and antifibrinolytic mediators of the cytokine storm, and to replenish anticoagulant proteins and to reduce viremia [94–97]. The latter report of TPE in three critically ill children with H1N1 influenza–related acute respiratory distress syndrome showed that TPE is effective even in the later stages of cytokine storm. Importantly, TPE comes at the cost of eliminating protective antibodies and drugs, an issue to consider when managing infection by TPE.

As the risk of developing severe and even potentially fatal COVID-19 pneumonia is extremely high in patients harboring auto-Abs against type I IFN, eliminating these auto-Abs by TPE emerges as an attractive additional line of treatment in hospitalized patients. So far, the use of TPE for COVID-19 pneumonia has been limited to case series. Another case reported the successful use of TPE in a pregnant woman suffering from thrombotic thrombocytopenic purpura with SARS-CoV-2 [98–105]. In these reports from the initial phases of the pandemic, TPE was used empirically for management of the "cytokine storm" during the phase of critical illness [98, 99, 101–104, 106, 107]. In some patients, intravenous immunoglobulins or convalescent plasma from other patients was used to replace circulating antibodies. Although these cases provide anecdotal evidence of potential benefits in some patients with severe COVID-19, they have also raised concern about its general use as a "rescue therapy" for all such patients [108–110]. A prospective clinical trial is required to better define its use [111]. Interestingly, in one of the original reports where TPE was used, the authors demonstrate a reduction in circulating antiphospholipid antibodies [103]. In light of the findings from COVIDhge [4], TPE can be considered specifically in those with demonstrable auto-Abs to type I IFN. Proof of concept for this mechanism-based use of TPE in severe COVID-19 has been recently reported [112]. Interestingly, the depletion of anti-IFN-abs by TPE was not accompanied by a depletion of anti-SARS-CoV-2 IgG [112]. Given the constellation of reports to date, the optimal use of TPE in COVID-19 needs to be better defined, including number of sessions needed and choice of volume replacement, but it appears to be best aimed at hospitalized patients with moderate-to-severe/critical disease who harbor anti-type I IFN auto-Abs. As stated above, the feasibility of this approach is contingent on the availability of a certified assay to detect and quantify neutralizing auto-Abs to type I IFN.

Type I IFN: Almost 50 Years of Therapy with IFN-α and IFN-β in Various Diseases

Type I IFN production, amplification, and response contribute to antiviral innate and intrinsic immunity. The first clinically successful use of type I IFN in humans dates back to 1973 and pertained to viral respiratory infections [113]. Type I IFNs were thereafter proposed as treatment of several other viral infections, especially chronic hepatitis C (HCV) and hepatitis B (HBV) virus infections. Recombinant IFN-α2 was first used in HCV treatment in 1986 [114]. Pegylated IFN-α2 (PEG-IFN-α2), allowing sustained blood levels, was introduced in the early 2000s and became standard treatment for chronic HCV infection until the appearance of direct-acting antivirals [115]. At present, PEG-IFN-α2 is still a treatment option in mild-to-moderate chronic hepatitis B patients. IFN-α2a and IFN-α2b are also used as an adjuvant in cancer treatment, such as certain leukemias (e.g., hairy cell; chronic myeloid) and Kaposi's sarcoma [116], based on its anti-proliferative, anti-angiogenesis, and immunomodulatory actions. Recombinant IFN-β1a and IFN-β1b, which exert effects similar to those of IFN-α2, have also been used therapeutically. IFN-β1a is a standard treatment for relapsing-remitting multiple sclerosis (MS) since the 1990s [117–119]. Short-term IFN-α2 treatment is associated in 20–30% with self-limiting flu-like symptoms. Long-term IFN-α2 treatment is associated with various side effects including (% affected; onset) fever (20–30%; 4–6 h after injection; self-limited); asthenia (60–90%; 3 months); psychiatric manifestations with depression and suicidal ideation (5–60%; 3 months); and thyroid autoimmunity (3–6%; median 17 weeks) [120–122]. Adverse reactions to IFN-β are similar to those of IFN-α [118]. In addition, long-term treatment with either molecule may illicit neutralizing anti-drug antibodies that can adversely affect treatment, as first reported in a patient receiving IFN-β for nasopharyngeal carcinoma [123–126]. These idiosyncratic reactions may be polygenically driven [127]. In all, short-term IFN-α or IFN-β treatment appears safe with little side effects and has proven efficient in the treatment of certain viral infections.

IFN-α2 in Past and Current COVID Trials

In the context of COVID-19, a NIH-issued guideline advises to restrict the use of IFN to clinical trials. Understandably, based on type I IFN's direct inhibitory effects on viral replication and indirect immunomodulatory effects, and based on its antiviral experience, IFN-α was one of the first drugs to be repurposed during the ongoing pandemic [128]. Only a few studies, and no randomized double-blind placebo-controlled trials (DBRCT), using IFN-α2 as a treatment have been published (Table 1). In a retrospective study, 242 of 446 hospitalized patients with severe COVID-19 received aerosolized

Table 1 Observational and interventional studies using type I IFN therapy

IFN	Study registry	Objective	Controlled trial	Country multi/ single center	Route	Daily dose	Dosing regimen	No. of patients
IFN-α1a	NA	Efficacy in reducing mortality of aerosolized IFN-α1a	*NA*	China	inhaled nebulized	NA	NA	446
IFNα-2b	NA	Efficacy of IFN-α2b in reducing the time to - PCR	*NA*	China	Inhaled nebulized	IFN-α2b (5 mU), arbidol (200 mg), both	IFN bid, arbidol tid	77 (7/24/46 per arm)
IFNβ-1a	NCT04385095	Efficacy and safety of inhaled nebulized interferon β -1a (SNG001) for the treatment of patients admitted to hospital with COVID-19	Randomized, double-blind, placebo-controlled, phase 2 pilot trial	UK multi-centric: 9 centers	Inhaled nebulized	6 MIU or placebo	Daily × 14 days	SNG001: 50 placebo: 51
IFNβ-1a	NCT04315948	Mortality trial of four repurposed antiviral drugs - remdesivir, hydroxychloroquine, lopinavir, and interferon β-1a	WHO's Solidarity Trial	International multi-centric: 405 hospitals in 30 countries	mainly s.c.	s.c. IFN: 44 μg or i.v. IFN: 10 μg	s.c. IFN: 3 doses in 6 days i.v. IFN: daily for 6 days	IFN: 2050 control: :2050
IFNβ-1b	NCT04276688	Study benefit of adding combined IFNβ+ ribavirin to standard care with LPV/r	Randomized open-label phase 2 trial	China (Hong Kong) multi-centric n=6	s.c.	Combined group: 8 MIU + ribavirin 400 mg	IFN: alternate days × 3 days/ribavirin: every 12h	Combined: 86 control: 41
IFNβ-1a	IRCT20100228003449N28	Compare 2 arms: IFNβ vs. control	Randomized	Iran single center	s.c.	44 μg	3 times per week × 2 weeks	IFN: 42 control: 39
IFNβ-1b	IRTC20100228003449N27	compare 2 arms: IFNβ vs. control	Randomized	Iran single center	s.c.	250 μg	1 dose every other day × 2 weeks	33 per arm
IFNβ-1a	IRCT20151227025726N12	All treated	No	Iran single center	s.c.	44 μg	1 dose every other day × 10 days	20
IFNβ-1b	-	All treated	no	France single center	inhalation	300 μg (lung delivery 10%)	12 days	4
IFNβ-1b	-	All treated	no	Korea single center	N.R.	N.R.	3–16 days	5
Ongoing trials COVID-19								
PEG-IFN-α2b	NCT04480138	Compare change in clinical status with or without IFN-a2b	Multicenter open-label randomized comparator controlled	Mexico, Multicenter	s.c.	1 mcg/kg	d1 and d8	40
IFN-α 1b	NCT04320238	To compare new-onset COVID-19-related symptoms at 6w from baseline	No placebo	China	i.n.	2–3 drops	4 t/day	nr
IFN-α	NCT04320238	To compare new-onset COVID-19-related symptoms at 6w from baseline	No placebo	China	i.n.	2–3 drops	4t/day	nr
IFN-α 2b	NCT04579518	To determine safety of iv rintatolimod with or without iv IFN-α2b	Open label	USA	i.v.	Dose escalation	d1, d3or4	44
IFN-α1β	NCT04293887	Efficacy and safety of IFN-α compared to SOC for hospitalized adult patients with COVID-19	Multicenter randomized open-label blank controlled multistage clinical trial	China	Nebulization	10 mcg	bid, 10 days	328
IFN-α	NCT04534725	(ARM1) Compare incidence of COVID-19 in cancer patients on prophylaxis with IFN-α	Sequential multiple arm randomized trial	Austrialia, multicenter	i.n.	nr	daily	2282 estimated
IFN-α			Sequential multiple arm randomized trial	Austrialia, multicenter	i.n.	nr	daily	2282 estimated

Table 1 (continued)

		(ARM2) Compare incidence of COVID-19 infection in cancer patients on post-exposure prophylaxis y/n with IFN-α					
IFNβ-1a	NCT04492475 ongoing	Compare combination of IFNβ-1a + remdesivir vs. remdesivir alone. Evaluate safet and efficacy	ACTT-3 trial randomized double-blind placebo-controlled phase 3 trial	NIAID USA multi-centric n=100	s.c.	44 μg	4 doses on days 1, 3, 5, and 7 while hospitalized	1000
IFNβ-1a	NCT02735707 universal trial no. U1111-1189-1653	Compare diverse immunomodulatory treatment (IFNβ among them)	REMAP-CAP trial https://www.remapcap.org/	International mullti-centric				> 4000
IFNβ-1a	NCT04449380	Compare IFNb-1a+ standard care vs. standard care alone	INTERCOP trial randomized, controlled, open-label, phase II trial	Italy mono-centric	s.c.	44 μg (12 MIU)	3 times × week at least 48h apart, for 2 weeks	126 random-ized 2:1 to IFNβ-1a
IFNβ-1a	NCT04521400 ongoing	Compare high- vs. low-dose IFNβ	Randomized open-label controlled 2-arm parallel group; phase 2a trial	Iran single center		Arm 1: high-dose IFN arm 2: low-dose IFN		Intention to treat: 50 patients per arm
Previous studies								
IFNβ-1a	NCT02622724	Efficacy and adverse events of IFNβ in patients with moderate ARDS	Randomized double-blind parallel-group trial	E.U. Multi-center n=74 ICU in 8 countries	i.v.	10 μg IFNb vs. placebo	Once daily × 6 days	IFN: 144 placebo: 152
IFNβ-1b	NCT02845843	Combined treatment with recombinant IFNβ-1b and LPV/r reduces mortality among patients with MERS	Randomized adaptive double-blinded placebo-controlled trial	Saudi Arabia multi-centric n=9 sites	s.c.	IFNβ: 0.25 mg (8 MIU) placebo: saline	Alternate days for 14 days	IFN:43 placebo:52

IFN	Sex (%men)	Age (y) mean (SD or range)	Other therapy	Inclusion criteria	Hospitalization days mean (range or SD)	Result	Adverse events	Ref
IFN-α1a	53.2	50y	Umifenovir/LPV/r	All admitted patients with confirmed SARS-CoV-2 by PCR	N.R.	Early IFN-α1a < 5d:reduced in hospital mortality	N.R.	[129]
IFNα-2b	0-20-11%	41 (27–68)- vs. 40 (25–80) vs. 64 (37–73)* %	Antibiotics	All admitted patients with confirmed SARS-CoV-2 by PCR	21.1 vs. 27d vs. 20.3d/all IFN vs. arbidol : 20 days	IFN-α2b: time to (-) PCR significantly shorter	NR	[130]
IFNβ-1a	SNG001: 62 placebo: 56	SNG001: 58 (15) placebo: 57 (12)		All eligible participants had to have a confirmed SARS-CoV-2 test result. Exclusion criteria included inability to use a nebulizer with a mouthpiece (e.g., ventilated patients and patients in intensive care); and pregnancy		Patients who received SNG001 had greater odds of improvement and recovered more rapidly from SARS-CoV-2 infection than patients who received placebo, providing a strong rationale for further trials	Headache: 15% patients in SNG001 group and 10% in placebo group. There were 3 deaths in the placebo group and none in the SNG001 group	[131]

Table 1 (continued)

IFNβ-1a	IFN: 64 control: 62	No difference in age distribution between IFN and control groups	No other trial treatments	Eligible patients were 18 years of age or older, were hospitalized with a diagnosis of Covid-19, were not known to have received any trial drug, were not expected to be transferred elsewhere within 72 h, and, in the physician' view, had no contraindication to any trial drug		Interim results: these drug regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. IFN regimens were discontinued for futility on October 16,2020		[16]
IFNβ-1b	Combined: 52% control:56%	Combined: 51 (31–61) cont:52 (34–63)	All received LPV/r	Treatment initiated <7 days from symptom onset	Combined: 9 (7–13) control: 15 (9–16)	The combination group had a significantly shorter median time from start of treatment to negative nasopharyngeal swab than the control group	No difference between groups	[132]
IFNβ-1a	IFN: 52% control: 56%	IFN: 57 (47–67) cont:61 (50–70)	LPV/r or atanazavir/r & HCQ & other drugs (no differences between groups)	Severe COVID-19: hypoxemia or hypotension or renal failure or neurologic disorders or thrombocytopenia, or severe gastrointestinal symptoms	IFN: 15 (8) control:12 (7)	Time to clinical response was no different. 28-day mortality was lower in the IFN group 19% vs. control group 17%. Early administration significantly reduced mortality	Psychiatric problems in 4 patients of the IFN group	[133]
IFNβ-1b	IFN: 61% control: 58%	IFN: 60 (47–73) cont:61 (50–71)	LPV/r or atanazavir/r& HCQ	First 48h after admission with O2 sat<93% PaO2/FiO2 < 300 mmHg	IFN:11 (9–13) control: 13 (10–17)	Time to clinical improvement was shorter in the IFN group (p=0.002). ICU admission rate higher in the control group (p=0.04)	N.R.	[134]
IFNβ-1a	80	58 (13)	LPV/r & HCQ	RR>30 breaths/min or O2 sat<90% or PaO2/FiO2 < 300 mmHg	17 (14–25)	No deaths or significant adverse events	N.R.	[135]
IFNβ-1b	75	59 (5)	HCQ and/or antibiotics & (in some patients: LPV/r & corticosteroids & vitamin C)	ICU/severe ARDS (PaO2/FiO2 < 100 mmHg)	33 (22–58)	3 patients improved at day 15	N.R.	[136]
IFNβ-1b	80	60 (14)	LPV/r, HCQ, corticosteroids	N.R.	32 (16–41)	3 patients deteriorated and were rescued with corticoids	N.R.	[137]
Ongoing trials COVID-19								
PEG-IFN-α2b		>18y	SOC	Laboratory confirmed Moderate SARS-CoV-2 infection. Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest X-ray, CT scan, etc.), SpO2 >93% and RR< 30/min	Change in clinical status by day 14			
IFN-α 1b		nr	NA	Medical staff in non-isolated general wards or laboratories, not in direct contact with COVID-19 patients		Number of infections		
IFN-α								

Table 1 (continued)

		Thymosinα sc 1 × per week	Medical staff in isolated wards in direct contact with COVID-19 patients			
IFN-α 2b		Rintatolimod: ds RNA designed to mimic viral infection	Cancer and mild-to-moderate COVID-19 (active therapy or within 6 months - no HSCT or active leukemia) - not specified within how many days from onset symptoms	Kinetics of viral load in nasopharyngeal swabs up to 30 days post-initiation		
IFN-α1β			Age > 18y, COVID-19 pneumonia, time between onset of symptoms and enrollment 7 days			
IFN-α	>18y		> 18y, any hematological or solid tumor, cancer therapy within the last 12 months	na	Number of infections	
IFN-α	>18y		> 18y, any hematological or solid tumor, cancer therapy within the last 12 months, exposed to known COVID-19 case within last 72h (15 min face to face, 2h in close space, household contact)	na	Number of infections	
IFNβ-1a		All patients will receive remdesivir 200 mg iv. On day 1 & 100 mg once-daily while hospitalized for up to a 10-day total course	Laboratory confirmed SARS-CoV-2 infection. Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest X-ray, CT scan, etc.), OR SpO2 <= 94% on room air, OR Requiring supplemental O2, among other		Primary outcome is time to recovery by day 29	https://clinicaltrials.
	> 4000			The trial is multifactorial as it tests multiple interventions	Patients admitted to ICU with acute respiratory insufficiency due to suspected pneumonia	The trial generates estimates of superiority, inferiority, and equivalence between regimens on the primary outcome of 90-day mortality, stratified by presence or absence of concomitant shock and proven or suspected influenza infection
IFNβ-1a		No other anti-viral drugs will be used as part of the regimens, both in the control and the intervention arms	Patients with positive swab detection of SARS-CoV-2, radiological signs of pneumonia, and mild-to-moderate disease		The primary outcome is the time to negative conversion of SARS-CoV-2 nasopharyngeal swabs. Secondary outcomes include improvement or worsening in a clinical severity	[139]

Table 1 (continued)

						score measured on a 7-point ordinal scale, among others		
IFNβ-1a			All patients will receive LPV/R	SPO2<93% or RR> 24 + one of the following manifestations: B.T<37.8 °C or cough, or shortness of breath or nasal congestion/discharge, or myalgia/arthralgia or diarrhea/vomiting or headache or fatigue on admission		Primary outcome: time to clinical improvement Secondary outcome: (a) mortality at the end of the study; (b) Improvement of SPO2 during hospitalization; (c) duration of hospitalization; (d) incidence of mechanical ventilation		[140]
Previous studies								
IFNβ-1a	IFN: 71 placebo: 60	IFN: 58 placebo: 58		Meeting ARDS criteria in 24h and first dose drug administration within 48h of ARDS diagnosis	IFN: 28 (24–28) placebo: 28 (22–28)	No significant difference in 21-day mortality between the IFNb group and placebo group	28% adverse events in the IFN group and 22% in the placebo group	Ranieri et al., 2020
IFNβ-1b	IFN: 72 place-bo:85	IIFN: 56 (43–67) placebo: 56 (44–67)	All received oral LPV/r	Hospitalized adults with laboratory-confirmed MERS with evidence of acute organ dysfunction related to MERS	Death by day 90 (%) IFN: 28 placebo: 44	A combination of recombinant interferon β-1b and lopinavir-ritonavir led to lower mortality than placebo among patients who had been hospitalized with laboratory-confirmed MERS. The effect was greatest when treatment was started within 7 days after symptom onset	Serious adverse events occurred in 4 patients (9%) in the intervention group and in 10 (19%) in the placebo group	Arabi et al., 2020

IFN-α2b. In 89%, nebulized IFN-α2b was initiated within 5 days of admission, which was associated with reduced mortality. Late initiation of nebulized IFN-α2b therapy was associated with increased mortality [129]. A prospective exploratory trial in hospitalized patients compared inhaled IFN-α2b with or without umifenovir, a broadly acting anti-viral, to umifenovir alone [130]. IFN-α2b was only included as a treatment arm when administered within 8 days of admission. The time to negative PCR was significantly shorter in patients receiving inhaled IFN-α2b [130]. Other trials included IFN-α2 in treatment arms with multiple drugs, including Chinese traditional medicine (Table 1). Overall, there has been a trend towards shorter duration of hospitalization and shorter time to negative SARS-CoV-2 PCR in patients admitted with COVID-19 pneumonia and treated with IFN-α2; however, interpretation of the data is hampered by the lack of a rigorously conducted DBRCT. Several protocols are currently recruiting hospitalized COVID-19 patients to study the efficacy and safety of administration within 7 days of symptom onset of s.c., i.v., or nebulized IFN-α2 (Table 1). Also, several trials will assess the efficacy of intranasal or nebulized IFN-α2 to prevent COVID-19 pneumonia. For instance, an Australian study will investigate the efficacy of IFN-α2 nose drops as a pre- or post-exposure prophylaxis in cancer patients. This trial in particular will be of interest as it can impact on the type I IFN deficiency in the first phase of COVID-19 infection, the time at which rapid induction of antiviral state is crucial.

IFN-β in COVID-19

In the context of highly pathogenic coronaviruses, IFN-β was reportedly more active than IFN-α, at least in vitro, in its antiviral activity [141–143]. Moreover, most patients with auto-Abs to type I IFNs had auto-Abs to the 13 individual IFN-α, including α2, and/or IFN-ω, but only 2% of them also had auto-Abs to IFN-β, IFN-κ, or IFN-ε [4]. Thus, therapeutic use of IFN-β should be a better choice than IFN-α from this viewpoint. Previous experience with another coronavirus, Middle East respiratory syndrome (MERS) virus, also supports this approach, with a clinical trial showing that IFN-β1b reduced mortality compared with placebo in hospitalized patients [144]. More trials with IFN-β than with IFN-α2 have been reported in the context of COVID-19 (Table 1). Several trials failed to show a beneficial effect. Oral favipiravir plus inhaled IFN-β failed to demonstrate any benefit when compared with hydroxychloroquine in terms of mortality, ICU admission, and inflammatory markers in hospitalized patients with moderate-to-severe COVID-19 pneumonia in an open-label randomized trial [145]. Similarly, the WHO Solidarity Trial failed to show a reduction in mortality in the s.c. and i.v. IFN-β1a treatment arms. However, about 50% of these patients received corticosteroids, which may have blunted the IFN effect [134]. Importantly, the adaptive COVID-19 treatment trial 3 (ACTT3) compared remdesivir plus placebo to remdesivir plus s.c. IFN-β1a and was halted prematurely in hospitalized patients receiving high-flow oxygen when interim data showed potential harm from subcutaneous IFN-β1a. In contrast, no harm was observed in patients receiving low-flow or no oxygen, in whom the efficacy of IFN-β1a is still being evaluated. On the other hand, some trials seem to show a benefit. A prospective, open-label, randomized single-center trial reported no significant difference in time to clinical response, but lower mortality at day 28 when s.c. IFN-β1a was added to treatment arms at median 10 days after onset of symptoms in hospitalized patients (Table 1) [133]. IFN-β1b s.c. plus lopinavir/ritonavir and ribavirin started at median 5 days in patients hospitalized with COVID-19 pneumonia resulted in shorter time to negative PCR in the triple treatment arm versus the lopinavir/ritonavir alone [132]. In an open-label RCT including severe COVID-19 patients, time to clinical improvement was shorter in the IFN-β1b s.c. group ($p=0.002$) and ICU admission rate higher in the control group ($p=0.04$) [134]. Finally, in a double-blind RCT, daily inhaled IFNβ-1a for 14 days in admitted patients led to a faster and stronger clinical improvement on the WHO Ordinal Scale for Clinical Improvement compared with placebo [131]. The patients had a median duration of symptoms of 10 days at recruitment and IFN-β was given for 14 days and was well tolerated. More trials are on the way, focusing on either ventilated COVID-19 patients or ambulatory patients to study the impact of late and early (at home) intervention with IFN-β (Table 1). Overall, the trials are inconclusive, potentially due to the relatively late administration of IFNs.

A Proposal: Early IFN-β in the Outpatient Setting

The two-step pathophysiology model of severe COVID-19 pneumonia suggests that early administration of IFN-β at the onset of SARS-CoV-2 infection, or even prior to infection in exposed individuals, may halt disease progression [5]. Especially at risk are individuals above age 65 years and individuals of any age with genetic defects of the type I IFN response pathway or with neutralizing anti-type I IFN auto-Abs. Several lines of evidence point to advantages in using IFN-β. First, in vitro data indicate higher efficacy of IFN-β against highly pathogenic coronaviruses. Second, the trials with IFN-β in MERS support its use, without neglecting the need for caution raised by the ACTT-3 trial. Third and most importantly, the auto-Abs to type I IFN neutralized the 13 IFN-α and IFN-ω but very rarely IFN-β. Among individuals at risk, either (A) a close contact of an index case (i.e., exposed

but negative for SARS-CoV-2), (B) an asymptomatic infected subject, or (C) an ambulatory (mildly symptomatic) patient may benefit from early IFN-β administration, i.e., as soon as possible post-exposure or post-infection. Indeed, the peak viral load on nasopharyngeal swab occurs at or even prior to onset of symptoms [146]. These three groups need distinct clinical trials to assess the efficacy of early IFN-β therapy in mitigating disease and viral shedding, as well as safety. Individuals vaccinated adequately against the viral variant diagnosed in the contact or themselves may or may not be considered. Of course, this presumes that viral strain testing can be performed with a short turnaround time. As outlined above, IFN-β can be administered via several routes, including i.m., s.c. (Pegylated form), nebulized, or a combination thereof. Nebulized IFN-β is likely to be of benefit early pre- or post-infection, owing to its local effect, whereas s.c./i.m. acts systemically and is likely to be effective beyond the first days post-infection. Thus, one could envisage having trials of post-exposure prophylaxis by nebulized IFN-β acting locally for the duration of the incubation time (14 days) in group (A), combined with s.c./i.m. IFN-β for systemic action in groups (B) and (C). Alternatively, all three groups could receive a single s.c. injection of peg-IFN-β. The advantage of pegylated IFN-β is that a single subcutaneous injection is sufficient and can easily be given in the outpatient setting. This early intervention with IFN-β in individuals at risk may theoretically alleviate the lack of type I IFN signaling early post-exposure or post-infection, the first phase of COVID-19 disease, by rapid induction of an anti-viral state, and may mitigate the natural evolution of SARS-CoV-2 infection to potentially fatal disease.

Type III IFN: IFN-λ

The IFN-λ family of cytokines can be produced by a number of cell types, including macrophages and plasmacytoid dendritic cells, in response to viral stimulation [147]. Like the type I IFN, they can establish an antiviral state; however, they do so through a distinct receptor complex primarily expressed on epithelial cells, including those in the respiratory tract. Signalling by type I or type III IFN shares overlapping antiviral IFN-stimulated gene (ISG) expression [148], suggesting that IFN-λ may potentially substitute or complement type I IFN therapy. In support of the latter, in vitro (using primary human airway epithelial cells) and mouse model data demonstrate that IFN-λ (specifically, IFN-λ1a) reduces SARS-CoV-2 replication when used either prophylactically or therapeutically [149, 150]. Similar to what we propose with IFN-β, early outpatient treatment of persons infected with SARS-CoV-2 using peg-IFN-λ has been studied. Patients who were either within 7 days of symptom onset or at first positive test if asymptomatic were treated with a single s.c. dose of peg-IFN-λ or placebo (N=30 per group) [151]. Those receiving peg-IFN-λ demonstrated faster viral clearance by day 7. Treatment tolerance was similar to placebo. Although the study was not powered to look at clinical evolution, 5 (16.7%) in the placebo group and 1 (3.3%) in the peg-IFN-λ group required visit to the emergency room by day 14. On the other hand, another study with a similar design showed that peg-IFN-λ did not shorten the duration of viral shedding [152]. Differences in results between these two studies may be due to differences in baseline viral loads (58% of subjects with >6.0 log copies/ml in the former vs. 75% with <5.5 log copies/ml in the latter) as well as differences in SARS-CoV-2 antibody positivity at baseline (0% in the treatment group and 10% in the placebo group in the former vs. 25% in the treatment group and 46.7% in the placebo group in the latter).

Although additional studies are needed, these studies provide proof of principle that a single dose of adjunctive peg-IFN-λ can be administered early following infection, is well tolerated, and may provide enhanced virological clearance especially in those with high viral load or delayed seroconversion. Whether this treatment impacts hospitalization or transmission requires further investigation. However, several caveats are in place. First, there is currently no genetic or immunological evidence that insufficient IFN-λ immunity can underlie severe COVID-19 pneumonia. Second, prolonged IFN-λ signaling has been described to disrupt lung epithelial repair following viral infection more potently than IFN-α and -β [153]. Third, sustained type III IFN signaling in inflamed lungs led to increased susceptibility to bacterial infection, at least in a mouse model [154]. Thus, the epithelial distribution of IFN-λ receptors may be disadvantageous rather than helpful in limiting the effects of this IFN to the epithelia. Fourth, we are still in the learning curve on IFN-λ as a treatment, both in terms of safety and side effect profile, but also in terms of pharmacokinetics and pharmacodynamics, favoring the preferential use of IFN-β in future trials aimed at preventing evolution to severe COVID-19 in individuals at risk.

Conclusion

Insight that type I IFN defects underlie severe COVID-19 in at least 10% of patients challenges past, ongoing, and future trials and clinical treatment strategies. Here, we discussed how findings from the COVIDhge provide a rationale for targeted interventions during specific phases of COVID-19 pathogenesis. Early testing can identify individuals with defects in the type I IFN circuit, whether genetically or serologically mediated, who stand to most benefit from IFN-β therapy prior to or during the early viral replication phase. In addition, the efficacy of IFN-β therapy would not be anticipated to be affected by the infecting SARS-CoV-2 variant. Those hospitalized and found to harbor neutralizing auto-Abs to type I

IFN might benefit from TPE. Ideally, trials should be designed to specifically address these different treatment groups. Our findings also raise important questions about some of the current approaches being evaluated, e.g., the use of convalescent plasma and the use of Jakinibs. Finally, despite the advent of efficacious vaccines in the general population, patients with defects of type I IFN immunity may continue to remain at risk, for example, due to impaired innate responses in the face of emerging variants or to sub-optimal adaptive immunity. The ongoing work of our consortium, in conjunction with the recent promising results of IFN-β in treatment of SARS-CoV-2 infection, opens bold new avenues in the global fight against this pandemic.

Availability of Data and Materials Not applicable for this commentary.

Author Contribution DV, LA, PB, MC, AC, PG, FH, MC, DH, PS, AP, APu, LN, QZ, HS, JLC, and IM wrote the manuscript. DV, JLC, and IM edited the manuscript. All authors commented and approved the final version.

Funding D.C.V. is supported by the Fonds de la recherche en santé du Québec clinician-scientist scholar Junior 2 program.

L.D.N. and H.C.S. are supported by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Institutes of Health (NIH) (R01AI088364), the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866), a Fast Grant from Emergent Ventures, Mercatus Center at George Mason University, the Yale Center for Mendelian Genomics and the GSP Coordinating Center funded by the National Human Genome Research Institute (NHGRI) (UM1HG006504 and U24HG008956), the Fisher Center for Alzheimer's Research Foundation, the Meyer Foundation, the French National Research Agency (ANR) under the "Investments for the Future" program (ANR-10-IAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID), the French Foundation for Medical Research (FRM) (EQU201903007798), the FRM and ANR GENCOVID project, ANRS-COV05, the Square Foundation, *Grandir - Fonds de solidarité pour l'enfance*, the SCOR Corporate Foundation for Science, *Institut National de la Santé et de la Recherche Médicale* (INSERM), and the University of Paris.

PB is supported by the MD-PhD program of the Imagine Institute (with the support of the Fondation Bettencourt-Schueller). I.M. is a Senior Clinical Investigator at the Research Foundation – Flanders, and is chair of the CSL Behring Chair of Primary Immunodeficiencies at KU Leuven, by the KU Leuven C1 Grant C16/18/007, by a VIB GC PID Grant, by the FWO Grants G0C8517N, G0B5120N, and G0E8420N, and by the Jeffrey Modell Foundation. This work is supported by ERN-RITA.

Declarations

Ethical Statement; Consent to Participate; Consent to Publish No ethical approval required. Consent to publish not applicable. Consent to publish not applicable.

Competing Interests The authors declare no competing interests.

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