Interferon Gamma Therapy in a Novel Case of Homozygous Interferon Alpha/beta Receptor Alpha Chain (IFNAR1) Deficiency Infected With SARS-CoV-2

Shaghayegh Khanmohammadi

Tehran University of Medical Sciences

Nima Rezaei

Tehran University of Medical Sciences

Mehdi Khazaei

Bushehr University of Medical Science

Afshin Shirkani (✉ a.shirkani@bpums.ac.ir)

Bushehr University of Medical Sciences <https://orcid.org/0000-0002-0514-3620>

Research Article

Keywords: COVID-19, SARS-CoV-2, Coronavirus, IFNAR1 deficiency, Interferon gamma, IFNs

Posted Date: August 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-831284/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Interferons play a crucial role in antiviral immunity. Genetic defects in interferon receptors (IFNRs) can lead to the development of life-threatening forms of infectious diseases.

Case presentation: A thirteen-year-old boy with a novel mutation in interferon alpha/beta receptor subunit 1 (IFNAR1)(c.674-2A>G) was diagnosed with COVID-19. He had cold symptoms and a high-grade fever at the time of admission. He was admitted to the pediatric intensive care unit after showing no response to favipiravir. High-resolution computed tomography (HRCT) scanning revealed lung involvement of 70% with extensive areas of consolidation in both lungs. Antibiotics, interferon gamma (IFN- γ), remdesivir, methylprednisolone pulse, and other medications were started in the patient. However, remdesivir and methylprednisolone pulse were discontinued after the occurrence of hypertension and bradycardia in the patient. His general condition improved, and a few days later was discharged from the hospital.

Conclusion: We reported a COVID-19 patient who had a novel mutation in IFNAR1 and was treated with IFN- γ . Our findings and approach to managing this COVID-19 patient suggest that IFN- γ therapy could be an appropriate choice to treat patients with defects in IFN- α/β signaling pathways.

Introduction

Interferon alpha/beta receptor subunit 1 (*IFNAR1*), located on chromosome 21q22.11, encodes a type I membrane protein that, together with IFNAR2, compose interferon alpha/beta receptor (IFNAR) [1]. Generally, IFNAR2 has a higher affinity for ligands, but recent studies have shown that IFN- β has the tightest binding among IFNs, which is associated with IFNAR1 [2]. Activation of IFNAR by IFN- α and IFN- β leads to tyrosine phosphorylation of several proteins, such as Janus kinase 1 (JAK1), tyrosine kinase 2 (TYK2), signal transducer and activator of transcription (STAT) proteins, and the subunits of IFNAR themselves in JAK-STAT signaling pathway [1]. IFNAR1 interacts with TYK2, and IFNAR2 interacts with JAK1 and STAT proteins. Then, STAT proteins become transported to the nucleus and act as transcription factors inducing/suppressing expression of interferon-stimulated genes (ISGs) that are associated with the immune system [2]. STAT proteins play their aforementioned role by interferon regulatory factor 9 (IRF9) to form the ISG factor 3 (ISGF3) complex [3].

Type I interferons are mainly known for their antiviral activity. They play their role by several mechanisms, such as inhibiting viral replication in the early stages of infection, upregulating the effector function of immune cells, triggering the adaptive immune response, and increasing antigen presentation [4]. The production of type I interferons is triggered by toll-like receptors (TLRs) [5]. Individuals with mutations in interferons, their receptors or signaling pathway, and insufficient interferon production show an inadequate antiviral response to the viral infections, which leads to the development of the life-threatening form of the disease [6]. For instance, patients with mutated IFNAR show adverse reaction to vaccination with live attenuated vaccines, such as measles, mumps, and rubella (MMR), and yellow fever vaccine [7]. Investigations in individuals with coronavirus disease (COVID-19) showed that patients with

genetic defects in the TLR pathway or IFNAR are more prone to developing severe forms of COVID-19 associated pneumonia than others [5, 8]. Previously, type I interferons were administered to treat COVID-19 patients with a genetic defect in the production of type I interferon pathways, which improved their symptoms [9]. The result of a clinical trial showed that administration of IFN- β decreases the time to clinical improvement in COVID-19 patients [10]. Another study revealed the positive effect of interferon gamma (IFN- γ) (type II interferon) in patient with moderate COVID-19 [11]. Hence, interferons may be a potential drug for treating COVID-19 patients with inborn type I interferon immunity errors. However, IFNAR deficiency complicates the administration of IFN- α/β for patients with COVID-19 since they have impaired receptors for type I interferons. Considering this fact, we reported a novel case of homozygous IFNAR1 deficiency infected with SARS-CoV-2, who was treated with IFN- γ .

Case Presentation

A thirteen-year-old boy with IFNAR1 deficiency was admitted to Bushehr Khalij Fars Hospital, Bushehr, Iran, in April 2021. He presented with upper respiratory tracts infection symptoms, such as runny nose, itchy throat, and low-grade fever for 11 days, followed by sweating and high-grade fever in the last three days. The patient only had a history of meningitis after getting vaccinated for MMR at 12 months of age. He was a suspected case of COVID-19, confirmed by a positive COVID-19 polymerase chain reaction (PCR) test. The treatment was initiated with favipiravir; however, the patient showed no response to the therapy, and his symptoms worsened, including shortness of breath and persistent fevers. Therefore, he was admitted to the pediatric intensive care unit (PICU). The result of high-resolution computed tomography (HRCT) scanning revealed lung involvement of 70% with extensive areas of consolidation in both lungs and patchy consolidation in the base of the lungs (see Fig. 1). The result of his echo test was normal. The oxygen saturation (SpO₂) of the patient at the first emergency department visit was 94% but decreased to 90% within the first days after hospitalization.

After hospitalization, the patient received vancomycin, piperacillin, tazobactam, aspirin, famotidine, zinc, vitamin C, IFN- γ , remdesivir, and methylprednisolone pulse (30mg/kg). Two days after hospitalization, the patient's fever persisted, and the antibiotics were switched to colistin and teicoplanin, and caspofungin was added to his medications. Although the level of IL-6 was high in the patient's serum, tocilizumab was not initiated for the patient due to the prolonged prothrombin time (PT) and partial thromboplastin time (PTT) (see Table 1). Because of the critical condition of the patient, he received one dose (1gr/kg) of intravenous immune globulin (IVIG). The patient also received IFN- γ (50 μ g/m²) between the third and sixth days of hospitalization (4 doses).

Table 1
Laboratory results.

Test	Result	Ref. range/Unit	Test	Result	Ref. range
WBC	13.2→14.2→9.9	4.8–10.8 10 ³ /μL	K	4.2	3.5–5.5 mEq/L
RBC	4.5	4.5–6.5 10 ⁶ /μL	BUN	19	6–23 mg%
Hb	12	13.5–18 g/dL	Creatinine	0.9	0.7–1.4 mg%
PLT	244	150–450 10 ³ /μL	Calcium	9.3	8.6–10.3 mg/dL
ESR	70→89→70	0–15 m.m/h	Phosphorus	3.1	3.2–5.7 mg/dL
IL-6	36	< 6.6 pg/mL	ALT	49	5–40 IU/L
PT	14.6→17.2→16.1	11–14 sec	ALP	400	35–130 IU/L
PTT	47.7→38.1→38.1	25–40 sec	Bilirubin total	0.5	0.3–1.2 mg/dL
INR	1.36→1.24→1.16	0.8–1.2	Bilirubin direct	0.1	< 0.3 mg/dL
Na	136	136–145 mEq/L	CPK	53	10–120 μg/L
WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLT, platelet; ESR, erythrocyte sedimentation rate; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; IL-6, interleukin-6; BUN, blood urea nitrogen; ALT, alanine transaminase; ALP, alkaline phosphatase; CPK, creatine kinase					

On the fifth day of hospitalization, the patient had bradycardia and hypertension; however, the second echo test and cardiology consultation were normal. Atropine was prescribed for the patient to be used in case the heart rate falls below 40 beats/min. The eye examination showed no papilledema, but pseudotumor cerebri was suspected. Therefore, remdesivir and methylprednisolone pulse were discontinued. After the fifth day of hospitalization, his fever was reduced, and his general condition improved on the sixth day of hospitalization. The SpO₂ of the patient increased to 94% with nasal cannula oxygen therapy (with a flow of 6 liters/min). The antibiotic therapy was continued for ten days, and the patient received fresh frozen plasma (FFP) (10cc/kg) to treat his prolonged PT and abnormal international normalized ratio (INR). During hospitalization, the patient had recurrent panic attacks that led to a lower SpO₂ below 90%. Hence, the psychologist prescribed risperidone, $\frac{1}{4}$ pill every night.

Eight days after hospitalization, the patient had a good general condition and was moved to the ward from PICU. On the ninth day of hospitalization, the patient's SpO₂ was above 94% without oxygen therapy, and two days later, he was discharged from the hospital.

IFNAR1 deficiency

The presented case was born to consanguineous parents and had a sister who passed away after getting vaccinated for MMR. As mentioned before, the patient had a history of meningitis after getting

Loading [MathJax]/jax/output/CommonHTML/jax.js at led to his recurrent hospitalization due to fever twice a

year. The periodic neutropenia disorder was suspected in the patient. Therefore, to find the underlying genetic cause of the disease, whole exome sequencing (WES) was performed as previously described [7]. The result of WES (see **Table 2**) revealed a novel homozygous mutation in the *IFNAR1* gene at the splicing site of exon 6 (NM_000629 Exon6:c.674(-2b)A>G). The Sanger sequencing analysis indicated that the parents, as expected, were heterozygous for such mutation. However, given the function of IFNAR1, the high effect of splicing mutation and heterozygosity of parents, the causative effect of this mutation on the disease is highly suggested.

Discussion

In this case report, presented a COVID-19 case who had a novel IFNAR1 deficiency. COVID-19, caused by SARS-CoV-2, has been a global concern since its emergence in 2020 [12]. Patients with underlying medical conditions are at increased risk for severe manifestations of SARS-CoV-2. Individuals with impaired IFN response seem to develop a life-threatening form of COVID-19 [8, 13]. Investigations in COVID-19 patients with IFNAR1 deficiency showed that they have impaired response to IFN- α and IFN- β [8]. Thus, type I interferon administration in these patients may not have an effective outcome, and other treatment strategies should be considered for them.

We treated our IFNAR1 deficient patient, who was infected with SARS-CoV-2, with IFN- γ administration. IFN- γ is a type II interferon produced by activated T cells and natural killer cells that binds interferon-gamma receptor (IFNGR) complex protein, and consequently, activates JAK/STAT pathway [14]. The activation of JAK/STAT pathway leads to induction/suppression of the transcription of IFN- γ -regulated genes [15]. IFN- γ has several functions, including antiviral immunity, macrophage activation, T helper 1 (Th1)/Th2 balance, regulation of apoptosis, and increasing antigen presentation via major histocompatibility complex (MHC) I and MHC II pathway [14]. IFN- γ induces antiviral immunity via inhibiting viral entry, suppressing virus replication, inducing cytokine production by immune cells, and enhancing cytotoxic T lymphocyte killing activity and phagocytosis. Nevertheless, due to the pro-inflammatory nature of the IFN- γ , persistently high levels of IFN- γ can lead to the occurrence of cytokine storm [16]. A study by Gadotti *et al.* revealed that higher levels of IFN- γ could cause death in COVID-19 patients [16]. Therefore, IFN- γ is a double-edged sword in the management of COVID-19.

The pathway of type I interferon (IFN- α/β) and type II interferon (IFN- γ) substantially overlap. For instance, ISGF3 can be activated by both type I interferon and IFN- γ . Apparently, IFN- α/β and IFN- γ can crosstalk augment each other's functions [15]. Administration of type I interferon in patients with IFNAR1 deficiency is ineffective. Based on this fact, we considered IFN- γ therapy for our patient. It should be noted that we discontinued IFN- γ therapy after the sixth day of hospitalization since the persistently high levels of IFN- γ may lead to cytokine storm in the later stages of the disease [17].

As mentioned before, on the fifth day of hospitalization, our patient showed symptoms similar to Cushing's (bradycardia and hypertension) [18], which indicates increased intracranial pressure. The corticosteroid therapy was discontinued in the patient since pseudotumor cerebri is one of the side

effects of corticosteroids [19]. Unfortunately, Due to the patient's critical condition, further investigations for measuring intracranial pressure were not possible. Additionally, remdesivir was also discontinued because of its adverse cardiac effects, including bradycardia [20].

To the best of our knowledge, we reported the first case with novel IFNAR1 deficiency that is infected with SARS-CoV-2, and treated with IFN- γ . Our findings and approach to managing this COVID-19 patient suggest that IFN therapy could be an appropriate choice to treat patients with defects in IFN production and signaling pathways.

Declarations

Acknowledgements

This study was supported by a grant from Tehran University of Medical Sciences (98-3-205-46257)

Funding

This study was supported by a grant from Tehran University of Medical Sciences (98-3-205-46257)

Conflicts of interest

The authors declare that they have no conflict of interest.

Availability of data and material

All data of this study are included in this published article.

Code availability

Not applicable

Authors' contributions

Conceptualization: AS

Formal analysis and investigation: SK, NR

Writing - original draft preparation: SK

Writing - review and editing: NR, AS

Funding acquisition: NR

Imaging studies and patient examination: MK, AS

Supervision: AS

Loading [MathJax]/jax/output/CommonHTML/jax.js

All authors read and approved the final manuscript.

Ethics approval

This study is approved by the ethics committee at the Tehran University of Medical Sciences (Approval ID: IR.TUMS.CHMC.REC.1399.002)

Consent to participate

Not applicable

Consent for publication

Informed consent was obtained from the patient's father for publication of this case report and any accompanying images.

References

1. UniProt. *UniProtKB - P17181 (INAR1_HUMAN)*. Available from: <https://www.uniprot.org/uniprot/P17181>.
2. Schreiber G. *The Role of Type I Interferons in the Pathogenesis and Treatment of COVID-19*. *Frontiers in Immunology*, 2020. 11(2599).
3. McNab F, et al. Type I interferons in infectious disease. *Nat Rev Immunol*. 2015;15(2):87–103.
4. Murira A, Lamarre A. *Type-I Interferon Responses: From Friend to Foe in the Battle against Chronic Viral Infection*. *Frontiers in Immunology*, 2016. 7(609).
5. Khanmohammadi S, Rezaei N. Role of Toll-like receptors in the pathogenesis of COVID-19. *J Med Virol*. 2021;93(5):2735–9.
6. Duncan CJA, Randall RE, Hambleton S. Genetic Lesions of Type I Interferon Signalling in Human Antiviral Immunity. *Trends Genet*. 2021;37(1):46–58.
7. Hernandez N, et al. Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. *J Exp Med*. 2019;216(9):2057–70.
8. Zhang Q, et al., *Inborn errors of type I IFN immunity in patients with life-threatening COVID-19*. *Science*, 2020. 370(6515).
9. Lévy R, et al. IFN- α 2a Therapy in Two Patients with Inborn Errors of TLR3 and IRF3 Infected with SARS-CoV-2. *J Clin Immunol*. 2021;41(1):26–7.
10. Alavi Darazam I, et al. Role of interferon therapy in severe COVID-19: the COVIFERON randomized controlled trial. *Sci Rep*. 2021;11(1):8059.
11. Myasnikov AL, et al. [Interferon gamma in the treatment of patients with moderate COVID-19]. *Vopr Virusol*. 2021;66(1):47–54.

12. Khanmohammadi S, et al. SARS-CoV-2: An insight into detection tools. Infect Disord Drug Targets; 2021.
13. Hadjadj J, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science. 2020;369(6504):718.
14. Tau G, Rothman P. Biologic functions of the IFN-gamma receptors. Allergy. 1999;54(12):1233–51.
15. Schroder K, et al. Interferon- γ : an overview of signals, mechanisms and functions. J Leukoc Biol. 2004;75(2):163–89.
16. Gadotti AC, et al. IFN- γ is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. Virus Res. 2020;289:198171–1.
17. Cappanera S, et al. When Does the Cytokine Storm Begin in COVID-19 Patients? A Quick Score to Recognize It. Journal of clinical medicine. 2021;10(2):297.
18. Dinallo S, Waseem M, *Cushing Reflex*, in *StatPearls*. 2021, StatPearls Publishing.
19. Copyright ©. StatPearls Publishing LLC. Treasure Island (FL); 2021.
20. Ivey KJ, DenBesten L. Pseudotumor Cerebri Associated With Corticosteroid Therapy in an Adult. JAMA. 1969;208(9):1698–700.
21. Touafchia A, et al. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clin Microbiol Infect. 2021;27(5):791. .e5-791.e8..

Figures

Figure 1

Lung HRCTs on admission day (left) and a few days later during hospitalization (right); A. Axial HRCT, aortic arch level. Extensive consolidation in upper lobes is seen; B. Axial HRCT, subcarinal level. Patchy confluent consolidation is turning to ground glass attenuation on the second study; C. Axial HRCT, basilar area. There are a few nodular consolidations in the first study (arrows). Patchy confluent consolidations and ground glass opacities are noted on the second study