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LETTER TO EDITOR

IFN-α2a Therapy in Two Patients with Inborn Errors of TLR3 and IRF3 Infected with SARS-CoV-2

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We recently reported that inborn errors of the TLR3- and IRF7-dependent production and amplification of type I interferons (IFNs) confer a predisposition to life-threatening COVID-19 pneumonia [1]. Inborn errors of eight genes were found to be causal: five from the TLR3-dependent pathway of induction (*TLR3*, *TICAM1*, *UNC93B1*, *TBK1*, *IRF3*), and three governing type I IFN induction and amplification (*IRF7*, *IFNAR1*, *IFNAR2*). These inborn errors include autosomal recessive (AR) (*IRF7*, *IFNAR1*) and autosomal dominant (AD) disorders (*TLR3*, *TICAM1*, *UNC93B1*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, *IFNAR2*). Four of the disorders observed had not previously been described (AD UNC93B, IRF7, IFNAR1 and IFNAR2 deficiencies), whereas the other six (AR IRF7 and IFNAR1 deficiencies, and AD TLR3, TICAM1, TBK1 and IRF3 deficiencies) had previously been reported in patients with severe influenza pneumonitis, herpes simplex encephalitis (HSE), or adverse reactions to live attenuated viral vaccines [1]. These findings suggested that early type I IFN administration might be beneficial in selected patients known to harbor one of the inborn errors known to affect the production or amplification of type I IFN.

We recently identified two adults with a known AD IEI of type I IFN production and COVID-19. Patient 1 was a 25-year-old woman with AD TLR3 deficiency (c.1660C>T; p.Pro455Ser) [2, 3]. She had two episodes of HSE as a child (at the ages of 5 and 7 years), but had since suffered no further serious viral infections [3]. Aware of her predisposition to severe COVID-19, she contacted our unit within the first 2 days of symptoms, and was admitted. She reported headaches, dyspnea, cough, fatigue, low-grade fever, and anosmia/ageusia. Neurological examination was normal. Real-time PCR (RT-PCR) on a nasal swab collected on admission (day 2 of symptoms) confirmed a high viral load of SARS-Cov2 (Ct: 23). However, digital droplet PCR failed to detect the virus in the blood. Oxygen saturation was 97%, and physical examination was normal, with no signs of pneumonitis. A CT scan of the lungs also revealed no signs of pneumonitis. C-reactive protein (CRP) was below the threshold of detection, and a complete blood count (CBC) revealed mild lymphopenia (0.9×10^9/L). The patient received a single subcutaneous injection of 90 μg (1.5 μg/kg) Peg-IFN-α2a (Pegasys). RT-PCR on nasal swab 36 h after Peg-IFN-α2a administration showed that viral load had strongly decreased (Ct:35). The patient reported a partial resolution of anosmia within the next 48 h. She was discharged on day 9, with no symptoms other than asthenia and residual anosmia. An evaluation on day 14 was unremarkable.

Patient 2 (P2) was a 29-year-old woman with AD IRF3 deficiency (c.761-764del; p.Asp254Glyfs*3) who had suffered recurrent mucocutaneous HSV-1 infections, at intervals of about 1 month, since the age of 23 years. She was admitted 7 days after the onset of symptoms, including fever, fatigue, cough, odynophagia, headaches, diarrhea, and anosmia/ageusia beginning 24 h before admission. Physical examination was normal and oxygen saturation was 99%. RT-PCR on a nasal swab collected on admission confirmed the presence of a high viral load of SARS-Cov2 (Ct: 21). CBC was normal,

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and CRP was undetectable. A CT scan showed ground-glass opacities in her left lower lobe with posterior predilection affecting about 10% of the lungs compatible with COVID-19. The patient received 80 μg (1.5 μg/kg) Peg-IFN-α2a administered subcutaneously. P2 reported a resolution of symptoms, including anosmia/ageusia, within 48 h of IFN administration. She was discharged on day 12.

We report here the safety of a single subcutaneous injection of Peg-IFN-α2a in two patients with IEIs affecting the production of type I IFNs associated with a predisposition to severe COVID-19 [1]. The rationale for proposing IFN-α2a treatment to these two patients was based on (i) the impairment of type I IFN production by both AD TLR3 and IRF3 deficiencies [2–5]; (ii) the development of severe COVID-19, sometimes with a fatal outcome, in some patients with IEIs affecting type I IFN production [1]; (iii) the anosmia/ageusia in both patients, whose IEI predispose to HSE, and the tropism of SARS-Cov2 for the central nervous system, which together stressed a risk of neurological manifestations of COVID-19; (iv) the high susceptibility of TLR3-deficient fibroblasts to SARS-Cov2 in vitro, a phenotype rescued by exogenous type I IFN; (v) the diagnosis of these two patients with COVID-19 at a very early stage of clinical manifestations, placing both patients in the so-called first phase of COVID-19; and (vi) the known safety profile of a single dose of Peg-IFN-α2a. Our findings cannot be considered a formal demonstration of the efficacy of IFN-α2a therapy for COVID-19, but both patients reported a rapid resolution of the symptoms and signs present at admission following the administration of Peg-IFN-α2a. This observation suggests that patients with known IEIs affecting the TLR3- and IRF7-dependent production and amplification of type I IFN signaling may benefit from the very early administration of type I IFN. Furthermore, this observation suggests that, in trials of type I IFN-based regimens for treating SARS-CoV-2-infected patients at risk of developing severe disease, the earliest possible administration should be considered.

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