

Adjunctive treatment of disseminated *Mycobacterium avium* complex infection with interferon alpha-2b in a patient with complete interferon-gamma receptor R1 deficiency

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Abstract We report adjunct treatment of (interferon) IFN- α 2b (Intron-A) in a patient with complete interferon- γ receptor R1 (IFNGR1) deficiency suffering from disseminated infection with *Mycobacterium avium* complex (MAC) resistant to multiple anti-mycobacterial agents. A low dose of IFN- α 2b (3×10^6 units/m² three times weekly subcutaneously) successfully attenuated progressive hepatosplenomegaly and abdominal/retroperitoneal/pelvic lymphadenopathy, although the patient continued to be mycobacteremic. This is the first report of a complete IFNGR1 deficiency treated with adjuvant IFN- α 2b for disseminated MAC infection.

Keywords Complete IFNGR1 defect · Disseminated *Mycobacterium avium* complex infection · Interferon- α 2b

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Abbreviations

AEC	absolute eosinophil count
BCG	<i>Mycobacterium bovis</i> bacillus Calmette-Guérin
CNS	central nervous system
CT	computed tomography
EMSA	electrophoretic mobility shift assay
HSCT	hematopoietic stem cell transplantation
IFN	interferon
IFNGR1	interferon- γ receptor R1
IRF	interferon regulatory factor
IV	intravenously
IVIG	intravenous immunoglobulin
Jak	janus kinase
KO	knockout
MAC	<i>Mycobacterium avium</i> complex
MRI	magnetic resonance imaging
PBMCs	peripheral blood mononuclear cells
STAT	signal transducer and activation of transcription
TG	triglyceride
TP	total protein
TSH	thyroid-stimulating hormone
Tyk2	tyrosine kinase 2

Case history

A 12-month-old Hispanic female was transferred to our institution from a community hospital with a presumed diagnosis of tuberculosis, as suggested by a positive tuberculin skin test (12 mm of induration) and chest X-ray findings. Disseminated *Mycobacterium avium* complex (MAC) infection was subsequently diagnosed by positive blood cultures and isolation of MAC on cultures of bone

marrow and cerebrospinal fluid. The product of a term gestation, the patient's prenatal, natal, and early postnatal history was unremarkable. She was born to parents who are third cousins and emigrated from the Dominican Republic prior to her birth. She has two older healthy brothers. Her respiratory illness started in early infancy. She was hospitalized at 3 and 11 months of age elsewhere with diagnoses of community-acquired pneumonia and had been treated for wheezing under diagnosis of infantile asthma.

Following an unrevealing conventional immune work-up, aberrant production of T cell cytokines by the child's peripheral blood mononuclear cells (PBMCs) in response to T cell mitogens led to a diagnosis of complete interferon- γ receptor R1 (IFNGR1) deficiency by flow cytometry when she was 2 years old. She was found to have the homozygous mutation 726delC in IFNGR1, a deletion immediately before the trans-membrane domain, causing complete loss of interferon (IFN- γ) receptor 1 and complete loss of functional response to exogenous IFN- γ (data not shown).

Despite treatment with multiple anti-mycobacterial drugs, the patient continued to be mycobacteremic. At her fourth admission to our institute at 17 months of age, a computed tomography (CT) scan revealed massive mediastinal lymphadenopathy, bilateral lower lobe infiltrates with cavitation and early abscess formation, and marked hepatosplenomegaly. At her fifth admission at 21 months of age, she suffered a severe bronchospasm during bronchoscopy, resulting in prolonged intubation; a bronchoalveolar lavage specimen yielded MAC. Her sixth admission at 26 months of age was secondary to MAC dissemination in the central nervous system (CNS), initially presenting with a grand mal seizure. MAC was isolated from CSF and an magnetic resonance imaging (MRI) study revealed numerous small enhancing lesions scattered throughout the cerebral hemispheres bilaterally. A severe bronchospasm occurred a second time during MRI with sedation despite the use of different agents, requiring another period of prolonged intubation.

At each hospitalization, modification of a multi-drug anti-mycobacterial regimen temporarily stabilized her clinical condition. However, by 34 months of age, her MAC isolates were resistant to most of the anti-mycobacterial drugs *in vitro*. At her seventh admission (at 38 months of age), a right psoas abscess caused by MAC was treated with surgical drainage and continuation of anti-mycobacterial drugs consisting of two intravenous (IV) medications (amikacin and gatifloxacin) and three oral medications (ethambutol, azithromycin, and rifampin). At 40 months old, linezolid was added to the treatment regimen as a fourth oral medication, which was switched to IV administration later.

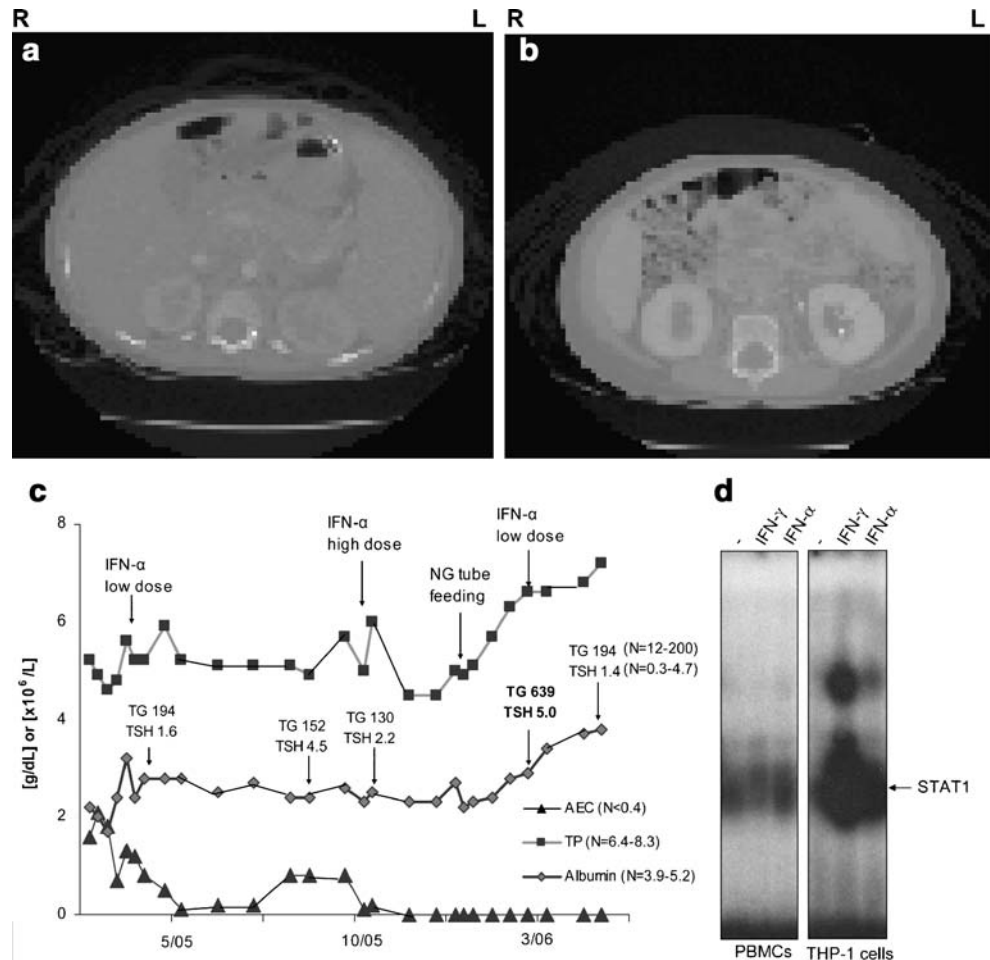
By the time of her eighth admission (at 41 months of age), her clinical deterioration became out of control with development of marked hepatosplenomegaly (spleen reaching to pelvis) and extensive retroperitoneal/abdominal/pelvic lymph-

adenopathy (Fig. 1a). She was experiencing respiratory distress and developed marked edema of the right leg (right thigh 4" larger in girth than left thigh). At that time, laboratory findings were significant for WBC count 14,400/mm³ with 44% band forms and 11% eosinophils, platelets 70,000/mm³, and hemoglobin 7.9 g/dl. The C reactive protein was elevated at 192 mg/l; the total protein was 4.6 g/dl with albumin 1.7 g/dl. Two oral medications that had been prescribed at the time (azithromycin and rifampin) were switched to IV administration in addition to three other IV medications (amikacin, gatifloxacin, and linezolid). She was also given increased amounts of intravenous gammaglobulin (IVIG) to improve hypoproteinemia and to potentially attenuate hypersplenism. IVIG was initially started at her fifth hospitalization to control hypersplenism and continued for cytomegalovirus prophylaxis. Nevertheless, her condition progressively deteriorated over the next 10 days culminating in the need for mechanical respiratory support.

At that point, adjunctive treatment of IFN- α was the only additional therapy we could offer. The rationale for this therapy was that IFN- α has the potential to activate downstream of IFN- γ signaling pathways shared by IFN- α and IFN- γ . After discussion, her parents consented to the initiation of adjunctive treatment of IFN- α 2b (3×10^6 units/m² three times weekly subcutaneously). Hepatosplenomegaly and lymphadenopathy slowly improved following initiation of IFN- α 2b treatment and the patient was discharged to home 4 weeks later. An abdominal CT scan taken 4 months after initiation of IFN- α 2b treatment revealed diminution of hepatosplenomegaly and retroperitoneal lymphadenopathy (Fig. 1b). The marked right inguinal lymphadenopathy, the right leg edema, and eosinophilia also resolved (Fig. 1c). However, her mycobacteremia and hypoproteinemia persisted despite reasonable oral intake of food (Fig. 1c). A higher dose of IFN- α 2b (6×10^6 units/m² three times weekly subcutaneously) did not further ameliorate her clinical condition; however, naso-gastric (NG) tube feeding with a free amino acid formula (EleCare) was effective in improving hypoproteinemia (Fig. 1c). With improvement of her nutritional status, triglyceride (TG) and thyroid-stimulating hormone (TSH) levels increased. Since these changes could represent adverse effects of IFN- α , her IFN- α 2b dose was lowered, following which both TG and TSH levels normalized (Fig. 1c). After initiation of IFN- α treatment, she was able to stay out of hospital most of the time except for two short periods of hospitalization. Her last hospitalization was in January 2006 at 51 months of age.

At 58 months, she remains mycobacteremic, but clinically stable with continuation of the multi-drug regimen consisting of three IV medications (linezolid, meropenem, and moxifloxacin) and three oral medications (azithromycin, ethambutol, and mefloquine), IVIG, thrice weekly IFN- α 2b subcutaneous injection, and NG tube feeding. Amikacin was replaced by

Fig. 1 **a** Computed tomography (CT) scan of the abdomen prior to (interferon) IFN- α 2b treatment revealed a markedly enlarged spleen and liver. **b** Hepatosplenomegaly was markedly improved 4 months after IFN- α 2b treatment. **c** Changes in levels of total protein (TP; g/dl), albumin (g/dl), and absolute eosinophil count (AEC; $\times 10^6/l$). *Arrows* indicate the initiation of the treatment indicated or measurement date of triglyceride and thyroid-stimulating hormone (TSH). **d** (Signal transducer and activation of transcription) STAT1 activation in response to IFN- γ (1,000 units/ml) and IFN- α (1,000 units/ml) in the patient's peripheral blood mononuclear cells (PBMCs). The patient's PBMCs (*left column*) and control acute monocytic leukemia cells (THP-1; *right column*) were treated with IFN- γ or IFN- α for 15 min and STAT1 activation was evaluated by electrophoretic mobility shift assay (EMSA), as described before [18]. The data shown are representative of three independent experiments. The *arrow* indicates the position of STAT1 complexes



meropenem secondary to progressive neuro-sensory hearing loss. The laboratory findings at 58 months old revealed: WBC count $11,500/mm^3$ with 7% band forms and 3% eosinophils, platelets $334,000/mm^3$, hemoglobin 10.6 g/dl, C reactive protein 12 mg/l, total protein 7.0 g/dl with albumin 3.8 g/dl, triglyceride 140 mg/dl ($N=16-200$), and TSH 3.6 μ unit/ml ($N=0.3-4.7$).

After improvement of her clinical condition, we tested the status of (signal transducer and activation of transcription) STAT1 activation in response to type I and type II IFNs. We consistently found an absence of STAT1 activation by IFN- γ in the patient's PBMCs (Fig. 1d). STAT1 activation was present in response to IFN- α (Fig. 1d), but the degree of STAT1 activation by IFN- α in PBMCs from the present case appeared to be less than in cells from healthy adult controls, irrespective of the in vivo doses of IFN- α (data not shown).

Discussion

Patients with defects of the IFN- γ and IL-12 circuit typically present with persistent infection with intracellular

microbes, which are poorly pathogenic in immuno-competent hosts [12, 21, 29].

The clinical phenotype can vary with individual genetic defects, but is very severe in patients with complete IFNGR1/R2 deficiency [7, 9, 12, 21, 30]. IFNGR1 deficiency is caused by allelic dominant and recessive mutations [8, 29]. Most recessive IFNGR1 deficiencies present complete lack of responses to IFN- γ , either by lack of IFN- γ receptor expression [3, 6, 13, 15–17, 20, 23, 26, 27, 30, 31, 33], as shown in this case, or by failure to recognize the ligand IFN- γ [2, 16]. Clinical features of IFNGR1 are characterized by a very narrow spectrum of opportunistic infections, mostly limited to environmental mycobacteria and *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), although serious infections with *H. capsulatum* and *Listeria monocytogenes* have been reported [8, 9, 12, 29]. As illustrated in the present case, patients with complete IFNGR1 deficiency are typically presented with early-onset, disseminated severe MAC infection [8].

Since patients with complete IFNGR1 deficiency reveal no functional response to IFN- γ , treatment of disseminated MAC infection in these patients is quite challenging [8, 12,

29]. In the studies of 22 patients with complete IFNGR1 deficiency, a third of patients died from their first recognized mycobacterial infection [8]. Among the survivors of the first infection, recurrence of mycobacterial infection was rapid after discontinuation of antibiotics, and they suffered from chronic disseminated mycobacterial diseases not resolved with anti-mycobacterial drugs, rendering a poor prognosis (4 out of 22 survivors; 18%) [9].

The only curative measure available for complete IFNGR1 deficiency is hematopoietic stem cell transplantation (HSCT) [28]. However, the successful HSCT is difficult to attain in complete IFNGR1 deficiency [14, 28]. Among 8 patients with IFNGR1 who received HSCT from the family donors, 4 patients died within 8 months of HSCT and only 2 patients who received non-T cell-depleted grafts from a sibling with identical human leukocyte antigen (HLA) remained in full remission from mycobacterial diseases 5 years after HSCT [28]. The third successful HSCT in the prolonged remission was only recently reported [4]. In the present case, the lack of a sibling with identical HLA and persistent disseminated MAC infection resistant to multiple anti-mycobacterial agents render the HSCT an unsuitable alternative therapeutic measure.

The IFN- γ receptor consists of two copies of the R1 and R2 subunits. IFN- γ binds to the R1 subunit, which is facilitated by the R2 subunit, resulting in phosphorylation of downstream signaling molecules including (janus kinase) Jak1, Jak2, and STAT1 [24, 29]. The type I IFNs such as IFN- α induce a wide variety of biological functions including antiviral, anti-proliferative, and cytotoxic activity [25]. The IFN- α receptor utilizes an overlapping signaling pathway that includes activation of Jak1, (tyrosine kinase) Tyk2, STAT1 as well as STAT2 [21, 24]. For example, STAT1 homodimers are involved in both IFN- γ - and IFN- α -mediated signaling, whereas the STAT1/STAT2/IRF9 (IFN regulatory factor 9) heterotrimeric transcriptional complex is mainly activated during IFN- α -mediated signaling [21, 23]. Patients with complete STAT1 deficiency reveal defects in responses to type I and type II IFNs, suffering from both mycobacterial and viral infection [5, 10], as also observed in STAT1 knockout mice [11, 22]. Thus, functional overlap may exist between IFN- α - and IFN- γ -mediated pathways and biological activities. We observed excessive production of both IFN- γ and IL-5 by the patient's PBMCs in response to T cell mitogens. Episodic eosinophilia and severe bronchospasms coincided with clinical exacerbations of the MAC infection in this patient. Eosinophilia has also resolved with IFN- α treatment. These beneficial effects of IFN- α could be attributed to its activation of STAT1 and downstream signaling pathways shared by IFN- γ .

On the other hand, the role of type I IFNs in mycobacterial infection does not appear to be substantial

in animal models. In IFN- α/β receptor knockout (KO) mice, aerosolized BCG exposure caused enhanced growth of BCG during the first 2–3 weeks compared with wild-type mice, but there was no difference in the BCG burden in the late phase [19]. The partial protective effects of type I IFN were attributed to augmented production of nitric oxide in the lung. In aged mice, the expression of early resistance to an infection with *Mycobacterium tuberculosis* was not attenuated in IFN- α/β KO mice [32]. In the presented case, we observed a lower level of STAT1 activation by IFN- α in the patients' PBMCs than in control cells. This could be the results of desensitization of the IFN- α receptor induced by the constitutive IFN- α treatment. However, such a decrease in IFN- α -induced STAT1 activation was not observed in hepatitis C patients who were responsive to constitutive IFN- α treatment [1].

These results indicate that activation via the STAT1 pathway may not be the major therapeutic effect observed in the present case. Alternatively, the attenuation of hepatosplenomegaly and lymphadenopathy experienced by this patient following IFN- α 2b treatment may reflect the anti-proliferative effects of IFN- α . Given the clinical responses observed in this case, we plan to continue the current IFN- α treatment as long as she tolerates it. However, further studies are required to delineate specific mechanisms of therapeutic action of IFN- α for treating patients with IFNGR1 deficiency. This case also illustrates the need for the careful monitoring of adverse effects associated with IFN- α as well as its failure to ablate persistent mycobacteremia.

Conclusion

The present case indicates the potential therapeutic benefits of exogenous IFN- α 2b as an adjunctive treatment for disseminated MAC infection in patients with complete IFNGR1 deficiency.

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