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Title Page

Allogeneic Hematopoietic Stem Cell Transplantation in Children with Mendelian Susceptibility to Mycobacterial Diseases Caused by Interferon Gamma Receptor 1 Deficiency and Literature Review

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Abstract

Purpose IFNGR1 deficiency is a rare primary immunodeficiency causing severe disseminated mycobacterial infections. HSCT is the only curative option, but reports of success are limited and optimal graft/TCD strategies remain unclear. We aimed to evaluate the safety and efficacy of peripheral blood stem cell transplantation with *in vivo* TCD for IFNGR1 deficiency using alternative donors.

Methods We retrospectively analyzed three pediatric patients with complete IFNGR1 deficiency who received HSCT at our center and performed a systematic literature review.

Results All three patients lacked HLA-matched sibling donors and received PBSC grafts with *in vivo* TCD (ATG and/or post-transplant cyclophosphamide) from alternative donors (10/10 unrelated, 5/10 haploidentical sibling, 8/10 mismatched unrelated). All achieved durable full donor chimerism (>99%) with no grade III-IV acute or extensive chronic GVHD. Manageable complications (PTLD, limited skin/joint/eye GVHD, pulmonary fungal infection) occurred without graft failure or transplant-related mortality. One patient who failed initial transplantation during active infection and elevated IFN-γ succeeded after infection control, underscoring the critical role of pre-transplant infection management.

Conclusion PBSC transplantation with *in vivo* TCD is safe and effective for complete IFNGR1 deficiency using alternative donors, expanding donor options and avoiding aggressive *ex vivo* TCD in this vulnerable population.

Key word: FNGR1 deficiency, Mendelian susceptibility to mycobacterial diseases (MSMD), Hematopoietic stem cell transplantation (HSCT)

Introduction

Mendelian susceptibility to mycobacterial diseases (MSMD) is a congenital immunodeficiency disorder characterized by selective vulnerability to intracellular pathogens, including mycobacteria, Salmonella, Listeria monocytogenes, and fungi(1). With regard to mycobacterial infections, affected individuals exhibit susceptibility not only to highly virulent strains such as Mycobacterium tuberculosis, but also to weakly virulent mycobacteria, including the Mycobacterium avium complex, Mycobacterium fortuitum, and Bacillus Calmette-Guérin (BCG)(2). The interferon-gamma (IFN-γ)/interleukin-12 (IL-12)/interleukin-23 (IL-23) signaling pathway plays a pivotal role in host defense against mycobacterial infection. To date, twenty-one genes have been associated with MSMD, most of which encode components of the IFN-γ/IL-12/IL-23 signaling pathway(3). Interferon gamma receptor 1 (IFNGR1), a transmembrane receptor for IFN-γ, was the first gene identified with pathogenic mutations linked to MSMD in 1996(4). IFNGR1 deficiency can be inherited in either an autosomal recessive or autosomal dominant manner; complete deficiency—almost always recessive—predisposes patients to severe, disseminated mycobacterial infections(5, 6). Hematopoietic stem cell transplantation (HSCT) represents the only curative therapeutic option. However, among patients with IFNGR1 deficiency, only over 10 cases of successful hematopoietic stem cell transplantation have been reported. Reporting such successful outcomes may contribute to refining HSCT protocols and post-transplant management strategies for these patients. In this report, we present three pediatric cases of IFNGR1 deficiency who underwent successful hematopoietic stem cell transplantation.

Method

A retrospective analysis was performed on the clinical data of three patients who successfully underwent IFNGR1 gene-targeted HSCT. Written informed consent was obtained from the legal guardians of all patients prior to treatment initiation. For the literature review, a systematic search was conducted in PubMed and Web of Science using the following strategy: In PubMed, the search terms were ((IFNGR1[Title/Abstract] OR IFNγR1[Title/Abstract] OR “Interferon gamma receptor 1”[Title/Abstract] OR “Interferon-γ receptor 1”[Title/Abstract]) AND (gene mutation[Title/Abstract] OR deficiency[Title/Abstract] OR variant[Title/Abstract]) AND (HSCT[Title/Abstract] OR “hematopoietic stem cell transplantation”[Title/Abstract] OR “bone marrow transplantation”[Title/Abstract])); in Web of Science, the corresponding search string employed Topic Search (TS) fields: TS=((IFNGR1 OR

IFNγR1 OR “Interferon gamma receptor 1” OR “Interferon-γ receptor 1”) AND (gene mutation OR deficiency OR variant) AND (HSCT OR “hematopoietic stem cell transplantation” OR “bone marrow transplantation”)).

Results

Case 1

A female infant born to non-consanguineous parents presented with recurrent fever, rash, and a left axillary mass approximately one month after birth. She had received the BCG. Laboratory tests revealed leukocytosis and elevated C-reactive protein (CRP). Immunoglobulin levels and lymphocyte subset analysis (CD markers) were within normal limits. Chest CT demonstrated bilateral pneumonia and a left axillary soft tissue mass. Blood metagenomic next-generation sequencing (mNGS) identified Mycobacterium tuberculosis complex(sequence count:3). After initial treatment with linezolid, ceftazidime, and intravenous immunoglobulin support, fever persisted despite rash resolution. Follow-up monitoring showed fluctuating white blood cell counts (WBC) (peaking at 33 × 10^9/L) and elevated CRP (max 120 mg/L), with sputum cultures revealing small amounts of Acinetobacter species. Cerebrospinal fluid acid-fast staining and tuberculin skin testing (PPD) were negative. Whole-exome sequencing (WES) was performed on the entire family. Subsequent therapy with linezolid, meropenem, and voriconazole achieved over two of afebrile status, after which antibiotics were discontinued and the patient was observed.

During drug withdrawal, WES revealed that the patient carried a homozygous mutation in INFGR1 (c.679dup, p.Thr227Asnfs*3). Shortly thereafter, the child experienced recurrent fever, left axillary lymphadenopathy, and BCG site swelling. Laboratory tests confirmed elevated WBC, CRP , ESR along with elevated procalcitonin (PCT) and ferritin. TORCH screen was positive for parvovirus B19 IgM. Sputum mNGS detected *Enterococcus faecalis*, *Acinetobacter baumannii*, and *Pneumocystis jirovecii*. QuantiFERON-TB testing was negative. Chest CT revealed pulmonary infiltrates bilaterally, multiple nodules in the right lung, subpleural air cysts, partial pleural thickening, and enlarged lymph node shadows in the mediastinum and left axilla. Axillary lymph node biopsy and gastric aspirate (3 day) were acid-fast bacilli negative. Antinuclear antibody was weakly positive (1:80); other autoantibodies negative. IFN-γ was markedly elevated (max 1075 pg/ml, normal <17.3 pg/ml). A four-drug anti-tuberculosis regimen (isoniazid, moxifloxacin, linezolid, and ethambutol) plus TMP-SMX (for *A.baumannii*.) was

initiated. After two weeks, the patient achieved full clinical recovery.

The INFGR1 c.679dup mutation leads to a frameshift that alters the amino acid sequence starting at position 227—changing threonine to aspartic acid—and results in premature termination of translation two codons downstream. Although this variant has previously been reported in patients with immunodeficiency in a compound heterozygous state , the present case reveals a homozygous mutation. Furthermore, protein expression analysis in this patient showed markedly reduced levels at only 5.6% of normal (laboratory data are not presented). Taken together with the clinical phenotype, these findings strongly support the pathogenicity of this mutation.

The patient received a 4-month anti-tuberculosis course, during which IFN-γ levels gradually normalized. A full myeloablative conditioning regimen was administered, consisting of fludarabine(Flu), busulfan (Bu), antithymocyte globulin (ATG), and thiotepa(TT). Graft-versus-host disease (GVHD) prophylaxis included mycophenolate mofetil (MMF), tacrolimus (TAC), and methotrexate (15 mg/m² on day +1 and 8 mg/m² on days +3, +6, and +12 post-transplantation). The patient underwent non-T-cell-depleted peripheral blood stem cell (PBSC) transplantation from a fully matched unrelated donor. Neutrophil engraftment was achieved on day +13 (>500 cells/mm³), and platelet engraftment on day +10 (>20,000 cells/mm³). Donor chimerism exceeded 99% on day +12 and remained >99% at 1-, 2-, and 6-months post-transplantation, with plasma IFN-γ levels consistently below 10 pg/mL.

Following engraftment, linezolid was discontinued due to leukopenia. One week later, fever and a scarred erythematous swelling in the left axillary lymph node developed. The anti-tuberculosis regimen was then intensified to a quadruple therapy by adding contezolid, after which temperature stabilized. Approximately one-month post-transplantation, the patient experienced recurrent fever. Serial monitoring revealed a progressive increase in EBV DNA load. Immunosuppression (MMF and tacrolimus) was withdrawn, and low-dose methylprednisolone (1 mg/kg/day, every 12 hours) was started for minimal immunosuppression. PET-CT showed widespread hypermetabolic lymphadenopathy (especially left axilla), hepatosplenomegaly and increased splenic metabolic activity, suspicious for post-transplant lymphoproliferative disorder (PTLD). Although family declined lymph node biopsy, Rituximab was initiated (375 mg/m² weekly for 2 weeks). After the first Rituximab dose combined with methylprednisolone, EBV DNA normalized within 5 days. Steroid was tapered, and a second Rituximab dose was administered. EBV DNA remained negative for 1.5 months. Methylprednisolone was gradually discontinued, and tacrolimus was reintroduced for GVHD prophylaxis. At +14 months, all

immunosuppressive and anti-tuberculosis medications were stopped. Now at 19 months post-HSCT (age 2 years and 4 months), the child has mild dry eye syndrome, attributed to chronic GVHD (cGVHD), with all other systemic stable.

Case 2

The patient was previously reported by our institution(7). The clinical presented at 3 months of age with fever, progressive left axillary lymphadenopathy, and local warmth. Parents were non-consanguineous. PPD was strongly positive at 72 hours. Lymph node fine-needle aspiration showed granulomatous inflammation. Genetic analysis identified a homozygous *IFNGR1* mutation (c.655G>A; p.Gly219Arg) with protein expression reduced to 19.8% of normal(8). Laboratory evaluation revealed mild leukocytosis: CRP, ESR, PCT, and ferritin were normal. Antinuclear antibody was weakly positive (1:100); other autoantibodies negative. CD markers, immunoglobulins, and immune profiling were unremarkable. Chest CT demonstrated bilateral pulmonary infiltrates and left axillary subcutaneous lesions with lymphadenopathy. Gastric aspirates (3 days) were negative for acid-fast bacilli. Based on the diagnosis of inherited immunodeficiency due to IFNGR1 mutation and anti-tuberculosis therapy (isoniazid, rifampicin, ethambutol) was initiated for BCG-related disseminated infection, with clinical improvement.

While on triple anti-tuberculosis therapy, he developed cervical lymphadenopathy. Aspiration revealed reactive lymphoid hyperplasia; acid-fast staining negative. He also had lower extremity pain and gait instability. Imaging identified multifocal bone lesions (parietal bone, thoracic vertebrae, right clavicle, bilateral ankle joints, proximal femur, and distal tibia). Bone biopsy, bone marrow culture, and metagenomic sequencing were negative. Following multidisciplinary evaluation, the patient was considered susceptible to mycobacterial infections, and levofloxacin was added to the treatment regimen. Subsequent clinical improvement was observed, with marked reduction in lymphadenopathy and stabilization of bone lesions. Due to perceived clinical stability and improved imaging findings, levofloxacin was discontinued during follow-up. However, symptoms recurred(bone pain, cervical lymph node enlargement) with imaging showing progression of hip and knee joint destruction. Blood cultures, metagenomic analyses, bone marrow smears, and cultures remained negative. A subsequent bone biopsy revealed fibrous tissue, increased microvessels, plasma cells, lymphocytes, histiocytic reaction, and a small number of multinucleated giant cells. Levofloxacin and linezolid were reintroduced

and continued until HSCT. Notably, peak IFN-γ was only 87.4 pg/ml (much lower than Case 1).

He received a myeloablative conditioning regimen (fludarabine , intravenous busulfan, ATG, and thiotepa). GVHD prophylaxis included MMF, tacrolimus, and post-transplantation cyclophosphamide (Cy, 50mg/kg on day +3). PBSC from an HLA-haploidentical sibling donor was transplanted, followed the next day by a supplementary 7/10 HLA-matched cord blood. Neutrophil and platelet engraftment were achieved on day +11 . Chimerism on day +12 exceeded 99% and remained sustained.

The anti-tuberculosis regimen was adjusted to a triple therapy including isoniazid, levofloxacin, and linezolid. More than one-month post-transplant, he developed acute GVHD (skin stage 3, overall grade II), prompting initiation of methylprednisolone. Following clinical improvement, methylprednisolone was gradually tapered. During steroid tapering and discontinuation, the child developed hemorrhagic cystitis confirmed by BK polyomavirus, which resolved with supportive care (including hydration, analgesia, IVIG). Corticosteroids were then fully discontinued.

Approximately four-month post-transplant, the patient presented with knee joint pain and swelling and fever. Patellar tap test was positive. Inflammatory markers were elevated. Blood NGS identified detected BK polyomavirus. Joint aspiration yielded turbid fluid: total cell 7,600 × 10^6/L, WBC 3,000 × 10^6/L (85% polymorphonuclear cells and 15% mononuclear cells), Rivalta positive, protein 35,375 mg/L, glucose 3.6 mmol/L, chloride 109 mmol/L. Cultures, acid-fast/fungal staining, and X-pert MTB/RIF were all negative. MRI showed resolution of prior sacroiliac and femoral lesions but new edema around distal femur/proximal tibia, joint effusion, and synovial thickening. Given the lack of microbiological evidence for active tuberculosis, meropenem was added to ongoing anti-tuberculosis therapy. After two weeks, inflammatory markers decreased and joint effusion significantly reduced.

Later, the child reported limb pain without overt swelling or restricted mobility. ESR was 63 mm/h. Ultrasonography showed synovial thickening in elbows and ankles. MRI confirmed resolution of previous marrow edema, suggesting persistent joint-related complications. At +16 months post-HSCT, immunosuppressants were discontinued; at +20 months, anti-tuberculosis medications were stopped. It

has been approximately 21 months since HSCT, the child is currently eight years and four months old, and he is well without joint pain or joint dysfunction.

Case 3

The patient developed recurrent fever, rash, and a left axillary mass approximately two months after birth. Her parents were not consanguineous, and she had received the BCG shortly after birth. At disease onset, she exhibited signs of significant systemic inflammation. Immunological evaluations, including CD marker profiling and immunoglobulin levels, were basically normal. The tuberculin-specific T-cell IFN-γ release assay was negative. Cytomegalovirus (CMV)-IgM was positive, while blood CMV-DNA was below 5.0×10^2 copies/mL. Cerebrospinal fluid analysis, bone marrow smear, blood cultures, and blister fluid cultures all yielded negative results. Brain MRI and chest and abdominal CT scans showed no abnormalities. Ultrasonography revealed multiple round hypoechoic masses in the left axilla, which gradually softened over time. An incision and drainage procedure was performed, followed by antimicrobial therapy with meropenem and linezolid for three weeks. Body temperature became stable. However, following discontinuation of medication, the patient experienced recurrence of fever and rash, accompanied by persistent elevation of inflammatory markers. blood mNGS detected Mycobacterium tuberculosis and human herpesvirus 5 (HHV-5). Sputum culture was positive for Candida albicans, and blood fungal culture identified Rhodotorula rubra. Chest CT demonstrated patchy infiltrates in both lower lung lobes. Serum interleukin-8 and IFN-γ was increased. Cerebrospinal fluid examination, including routine analysis, biochemical testing, culture, and mNGS remained negative. Family WES revealed compound heterozygous mutations in IFNGR1: c.77+5 (IVS2) G>C and c.188 (exon 3) C>A. Antituberculosis therapy was initiated with isoniazid, rifampicin, and ethambutol. During treatment, the patient developed hypoxemia requiring supplemental oxygen, and CRP levels continued to rise. Meropenem and linezolid were reintroduced, ganciclovir was added for antiviral coverage, micafungin was initiated for antifungal prophylaxis, and blood transfusion support was provided. With nasal cannula oxygen therapy, vital signs stabilized. Later, the child developed pallor, along with elevated liver enzymes, bilirubin, and bile acid levels, suggestive of drug-induced liver injury. Rifampicin was discontinued and replaced with moxifloxacin. Hepatoprotective and choleretic agents were administered, resulting in clinical improvement. Maintenance antituberculosis therapy was continued with isoniazid, ethambutol, and moxifloxacin.

The IFNGR1 c.77+5 (IVS2) G>C splice site mutation might disrupt normal mRNA processing, leading to exon skipping or abnormal transcription, while the c.188 (exon 3) C>A mutation leads to an amino acid substitution at position 63 from alanine to aspartic acid (p.A63D). Both variants were classified as PM2 (absent from population databases) and PP3 (multiple *in silico* tools predict deleterious effects on splicing or protein function). The c.77+5 G>C variant was inherited from the father (heterozygous), and the c.188 C>A variant was inherited from the mother (heterozygous), consistent with a compound heterozygous state. Furthermore, protein expression analysis in this patient showed markedly reduced levels at only 1.7% of normal (laboratory data are not presented). Taken together with the clinical phenotype, these findings strongly support the pathogenicity of these mutations.

The child continued to receive anti-tuberculosis therapy for approximately three months, during which the highest IFN-γ levels is 194 pg/mL. blood mNGS consistently detected CMV. Prior to transplantation, the patient developed diarrhea; stool metagenomic analysis revealed the presence of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae (ESBL+), carbapenem-resistant strains, norovirus, and CMV. Following initiation of ganciclovir in combination with meropenem for anti-infective treatment, along with symptomatic management, the gastrointestinal symptoms improved. Anti-CMV therapy with ganciclovir was maintained for nearly two weeks and continued throughout the stem cell transplantation procedure.

A fully myeloablative conditioning regimen was administered prior to transplantation, consisting of fludarabine, busulfan, and ATG. GVHD prophylaxis included MMF, cyclosporine(CsA), and methotrexate (MTX: 12 mg/m² on day +1, followed by 7 mg/m² on days +3 and +6) to prevent graft rejection. A peripheral blood stem cell transplant from a fully HLA-matched unrelated donor was performed. During the early post-transplant period, diarrhea recurred and was managed orally with vancomycin. However, despite discontinuation of immunosuppressive agents, chimerism levels remained persistently low, showing no significant increase until day +26 post-transplantation, at which point the level was still below 5%, indicating poor engraftment and consistent with implantation failure.

Subsequently, a second non-myeloablative conditioning regimen was initiated, comprising fludarabine (85 mg/m²) and cyclophosphamide (60 mg/kg). GVHD prophylaxis was maintained with MMF and cyclosporine. A second infusion of peripheral blood stem cells from the same unrelated donor was administered, containing 18.6×10^8 mononuclear cells per kg. On day +2 post-reinfusion, fever developed, with the escalation of antimicrobial therapy (mecamylamine, teicoplanin, and ornidazole),

body temperature subsequently turned normal and inflammatory markers showed improvement. Unfortunately, chimerism assessments on days +7 and +15 after reinfusion both indicated levels below 5%, confirming ongoing engraftment failure.

The child continued to be followed up and remained asymptomatic during this period. Approximately five months after the first transplantation, the patient underwent a second hematopoietic stem cell transplantation following a complete myeloablative conditioning regimen. This regimen included fludarabine, busulfan, ATG, and thiotepa, with GVHD prophylaxis consisting of MMF, cyclosporine, and methotrexate (15 mg/m² on day +1, and 9.5 mg/m² on days +3 and +6). A peripheral blood stem cell graft from an HLA 8/10-matched unrelated donor was transplanted. Concurrently, a 9/10 HLA-matched umbilical cord blood unit was co-transplanted to support engraftment. On day +8 post-transplantation, mesenchymal stem cells were infused as adjunctive therapy. Neutrophil engraftment was achieved on day +13, and platelet engraftment was confirmed on day +15. At approximately four months post-transplantation, the patient developed pulmonary infection, chest X-ray revealed a localized pleural reaction on the right side. CT scans showed multiple small patchy and nodular shadows. Although blood culture, G test and GM-assays was negative. the patient was treated with amphotericin B for nearly three weeks, after which CT scans showed signs of improvement. Subsequently, sequential antifungal therapy with posaconazole was initiated. All immunosuppressive and antifungal medications were discontinued one year after transplantation. The child, now four years and six months old, is doing well clinically at approximately three years and two months post-HSCT.

Literature Review

As of now, among the 12 articles that have reported on the use of hematopoietic stem cell transplantation for IFNGR1 deficiency, a total of 16 patients have been described before (figure 1)(9-20). However, only 8 patients succussed (Table 4), the majority of which selected fully HLA-matched siblings as donors, and no successful cases have opted for In vitro T-cell depletion treatment. The earliest summarized 8 case studies showed that among the 6 HSCT underwent T-cell depletion, 5 HSCT experienced implantation failure, 1 HSCT developed Epstein-Barr virus–induced lymphoproliferative syndrome and died(12). Haploid parents were selected as donors as well, and this approach was also attempted in two cases, but in the end, all the children failed to be implanted(12, 19). Otherwise, cases that were successfully implanted still had a high risk of infection (weakly virulent mycobacteria) and

complications related to the transplantation, which can lead to death(12, 14).

Discussion

The prognosis of children with MSMD caused by different genetic defects varies. Patients with complete IFNGR1 deficiency have a very poor prognosis, a third of recessive complete IFNγR1 patients died from their first recognized mycobacterial(5). The mutation types carried by case 3 have not been reported before, while the mutation carried by case 1 and 2 has been previously reported and is considered a pathogenic mutation. The protein expression levels of the three children in our study significantly decreased. Although, we did not conduct protein function assays to confirm whether the patients had partial or complete IFNGR1 deficiency, all three patients had early-onset BCG infection, and two of them had disseminated infection. At the same time, they also suffered from other severe opportunistic infections. Based on the clinical manifestations of these children, we believe that they all carry pathogenic mutations in the *IFNGR1* and are suitable for early HSCT.

Historically, HSCT for IFNGR1 deficiency was associated with low success rate, with graft failure and mortality predominating in patients who received T-cell-depleted grafts or underwent transplantation with active mycobacterial infection. Among the few successful cases, most used bone marrow or cord blood from HLA-matched sibling donors (MSD) and avoided *in vitro* TCD. In contrast, all three of our patients3 received peripheral blood stem cells (PBSC) grafts. Donor types included a 10/10 unrelated donor, a 5/10 haploidentical sibling, and an 8/10 mismatched unrelated donor (with cord blood co-infusion in two cases). None developed grade III-IV acute or extensive chronic GVHD, and all achieved durable full donor chimerism without graft failure. Manageable complications — PTLD, limited skin, joint, eye GVHD, pulmonary fungal infection —occurred but did not compromise survival or lead to transplant-related mortality. This suggests that, compared with bone marrow/cord blood, PBSC do not carry an unacceptable risk of GVHD in IFNGR1 deficiency; on the contrary, their advantages of rapid engraftment, abundant stem cell dose, and the option to combine with cord blood when necessary help control infections, promote immune reconstitution, and reduce graft failure. These findings indicate that with advances in transplantation techniques (including more precise infection control, individualized conditioning regimens, and effective GVHD prophylaxis), PBSC can safely extend curative treatment to IFNGR1-deficient children who lack an MSD or require rapid engraftment

Only 15–30% of children undergoing HSCT have access to an HLA-matched sibling donor (MSD)

(21, 22). In the absence of an MSD—whether using a mismatched related donor (MMRD) or matched unrelated donor (MUD)—TCD is commonly employed to mitigate GVHD. In IFNGR1 deficiency, however, the profound defect in IFN-γ-mediated immunity confers exceptional vulnerability to disseminated mycobacterial and other opportunistic infections, making the choice of TCD strategy particularly critical. TCD approaches are broadly divided into in vivo (e.g., ATG, post-transplant cyclophosphamide [PTCy]) and in vitro (e.g., TCRαβ/CD19$^+$ depletion, which have been applied in HLA-mismatched HSCT for children with inborn errors of immunity (IEI)(23, 24). A large EBMT registry study (306 pediatric IEI patients undergoing HLA-mismatched HSCT) directly compared in vitro TCRαβ/CD19$^+$ depletion versus in vivo PTCy. In vitro depletion achieved significantly lower grade III-IV acute GVHD (6% vs. 15%), but at the cost of higher adenoviremia (18.3% vs. 8.0%), primary graft failure (10% vs. 5%), and secondary HSCT (17.4% vs. 7.9%; all $P < 0.05$)(25). Notably, the literature review confirmed that among all previously reported successful HSCT cases for IFNGR1 deficiency, none employed *in vitro* TCD. In contrast, graft failure was uniformly observed when *in vitro* TCD was attempted. These observations underscore the particular unsuitability of aggressive *ex vivo* TCD in this vulnerable population.

Our three IFNGR1-deficient children all lacked an MSD. We deliberately selected in vivo TCD (ATG/PTCy) rather than in vitro TCD, based on two considerations: (1) these patients are already at high risk for infections and graft failure, and in vitro TCD would further increase viral reactivation and graft loss; (2) donor T cells are essential for engraftment and early anti-pathogen immunity. Despite using alternative donors —including a 5/10 haploidentical sibling and 8/10 mismatched unrelated donor with cord blood—all three achieved durable engraftments, with only manageable complications and no sever GVHD. Our experience supports that in vivo TCD—particularly PTCy-based regimens—is a safe, effective, and rational choice for IFNGR1 deficiency, offering a favorable balance between GVHD control, infection prevention, and engraftment success.

The research has found that the presence of high levels of IFN-γ in patients with IFNGR1 deficiency is one of the main factors leading to transplant failure. It has been proven that IFN-γ is a cytokine that inhibits hematopoietic generation in the body and can directly suppress the development and growth of heterologous hematopoietic stem cells that express normal IFN-γ receptors(26). Infection can directly trigger the production of IFN-γ, and mycobacteria are even stronger inducers of IFN-γ(27). Controlling infection and keeping the patient in a stable state without active infection is the most effective method to

reduce IFN-γ at its source. The third patient in this study failed the first transplantation, likely due to pre-transplant infection and an abnormally elevated IFN-γ level. After infection was controlled and IFN-γ normalized, the second transplantation succeeded. This underscores that controlling pre-transplant infection to lower IFN-γ is critical for successful HSCT in IFNGR1 deficiency.

In conclusion, this study provides valuable therapeutic experience for non-matched peripheral blood stem cell transplantation in the treatment of IFNGR1 deficiency. The combination of *in vivo* TCD (PTCy/ATG) and rigorous pre-HSCT infection control appears to overcome the historical barriers of graft failure and severe GVHD, even when alternative donors are used. These findings expand donor options for this ultra-rare disease and provide a rationale for avoiding aggressive *ex vivo* TCD in this vulnerable population.

Conclusions

In conclusion, we present three pediatric cases of complete IFNGR1 deficiency successfully treated with allogeneic HSCT using peripheral blood stem cell grafts and *in vivo* T-cell depletion (ATG and/or post-transplant cyclophosphamide) from alternative donors, including mismatched unrelated and haploidentical donors. All three patients achieved durable full donor chimerism without severe GVHD or transplant-related mortality. One patient who failed initial transplantation during active infection and elevated IFN-γ succeeded after infection control, underscoring that rigorous pre-transplant infection management to normalize IFN-γ is critical for success. These findings support the use of alternative donors and *in vivo* TCD, and provide a strong rationale for avoiding aggressive *ex vivo* T-cell depletion in this vulnerable population.

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Authorship Contributions The author contribution is as follows: X.W.Z conceived and supervised the study; L.L, P.W and W.J.J performed the data collection and analysis; L.L produced graphics and chart and wrote the original draft; P.W, W.J.J, H.S.W and X.W.Q provided clinical routine. W.J.W, X.C.W, and J.Q.S provided immunological expertise; L.L, X.W.Q, and X.W.Z performed the literature review; X.W.Z. and X.W.Q. revised the manuscript. All authors read and approved the final manuscript.

Data Availability The datasets generated and analyzed during this study are not publicly available due to patient privacy and ethical restrictions, but are available from the corresponding author on reasonable request. The literature review data are derived from previously published studies cited in the reference list.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Children's Hospital of Fudan University (No. 2017 159).

Consent to participate All patients' guardians provided written in-formed consent for enrollment in this study.

Consent to publish The authors affirm that human research participants provided informed consent for publication.

Competing interests The authors declare no competing interests.

Reference

1. Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, Markle J, et al. Mendelian susceptibility to mycobacterial disease: 2014-2018 update. Immunol Cell Biol. 2019;97(4):360-7.
2. Dalvi A, Bargir UA, Natraj G, Shah I, Madkaikar M. Diagnosis and Management of Infections in Patients with Mendelian Susceptibility to Mycobacterial Disease. Pathogens. 2024;13(3).
3. Khavandegar A, Mahdaviani SA, Zaki-Dizaji M, Khalili-Moghaddam F, Ansari S, Alijani S, et al. Genetic, immunologic, and clinical features of 830 patients with Mendelian susceptibility to mycobacterial diseases (MSMD): A systematic review. J Allergy Clin Immunol. 2024;153(5):1432-44.
4. Newport MJ, Huxley CM, Huston S, Hawrylowicz CM, Oostra BA, Williamson R, et al. A mutation in the interferon-gamma-receptor gene and susceptibility to mycobacterial infection. N Engl J Med. 1996;335(26):1941-9.
5. Dorman SE, Picard C, Lammas D, Heyne K, van Dissel JT, Baretto R, et al. Clinical features of dominant and recessive interferon gamma receptor 1 deficiencies. Lancet. 2004;364(9451):2113-21.
6. Sologuren I, Boisson-Dupuis S, Pestano J, Vincent QB, Fernandez-Perez L, Chapgier A, et al. Partial recessive IFN-gammaR1 deficiency: genetic, immunological and clinical features of 14 patients from 11 kindreds. Hum Mol Genet. 2011;20(8):1509-23.

7. Ying W, Liu D, Dong X, Wang W, Hui X, Hou J, et al. Current Status of the Management of Mendelian Susceptibility to Mycobacterial Disease in Mainland China. J Clin Immunol. 2019;39(6):600-10.
8. Zeng Y, Ying W, Wang W, Hou J, Liu L, Sun B, et al. Clinical and Genetic Characteristics of BCG Disease in Chinese Children: a Retrospective Study. J Clin Immunol. 2023;43(4):756-68.
9. Roesler J, Kofink B, Wendisch J, Heyden S, Paul D, Friedrich W, et al. Listeria monocytogenes and recurrent mycobacterial infections in a child with complete interferon-gamma-receptor (IFNgammaR1) deficiency: mutational analysis and evaluation of therapeutic options. Exp Hematol. 1999;27(9):1368-74.
10. Reuter U, Roesler J, Thiede C, Schulz A, Classen CF, Oelschlagel U, et al. Correction of complete interferon-gamma receptor 1 deficiency by bone marrow transplantation. Blood. 2002;100(12):4234-5.
11. Horwitz ME, Uzel G, Linton GF, Miller JA, Brown MR, Malech HL, et al. Persistent Mycobacterium avium infection following nonmyeloablative allogeneic peripheral blood stem cell transplantation for interferon-gamma receptor-1 deficiency. Blood. 2003;102(7):2692-4.
12. Roesler J, Horwitz ME, Picard C, Bordigoni P, Davies G, Koscielniak E, et al. Hematopoietic stem cell transplantation for complete IFN-gamma receptor 1 deficiency: a multi-institutional survey. J Pediatr. 2004;145(6):806-12.
13. Chantrain CF, Bruwier A, Brichard B, Largent V, Chapgier A, Feinberg J, et al. Successful hematopoietic stem cell transplantation in a child with active disseminated Mycobacterium fortuitum infection and interferon-gamma receptor 1 deficiency. Bone Marrow Transplant. 2006;38(1):75-6.
14. Edeer Karaca N, Boisson-Dupuis S, Aksu G, Bustamante J, Kandiloglu G, Ozsan N, et al. Granulomatous skin lesions, severe scrotal and lower limb edema due to mycobacterial infections in a child with complete IFN-gamma receptor-1 deficiency. Immunotherapy. 2012;4(11):1121-7.
15. Olbrich P, Martinez-Saavedra MT, Perez-Hurtado JM, Sanchez C, Sanchez B, Deswarte C, et al. Diagnostic and therapeutic challenges in a child with complete interferon-gamma receptor 1 deficiency. Pediatr Blood Cancer. 2015;62(11):2036-9.
16. Michniacki TF, Walkovich KJ, Frame DG, Vander Lugt MT. Interferon-gamma Receptor 1 Deficiency Corrected by Umbilical Cord Blood Transplantation. J Clin Immunol. 2019;39(3):257-60.
17. Bossi G, Errichiello E, Zuffardi O, Marone P, Monzillo V, Barbarini D, et al. Disseminated Mycobacterium Avium Infection in a Child with Complete Interferon-gamma Receptor 1 Deficiency due to Compound Heterozygosis of IFNGR1 for a Subpolymorphic Copy Number Variation and a Novel Splice-Site Variant. J Pediatr Genet. 2020;9(3):186-92.
18. Zerbe CS, Dimitrova D, Gea-Banacloche JJ, Kreuzburg S, Holland SM, Kanakry JA. Successful Matched Related Bone Marrow Transplantation in a Patient with Autosomal Dominant Interferon Gamma Receptor 1 Deficiency. J Clin Immunol. 2020;40(7):1045-7.
19. Patel S, Uppuluri R, Vellaichamy Swaminathan V, Ravichandran N, Melarcode Ramanan K, Raj R. Mendelian susceptibility to mycobacterial disease-Challenges in hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2020;67(5):e28187.
20. Labere B, Christian E, Kapadia M, Prockop S, McDonald DR, Johnston AM. A Novel Combination of Compound Heterozygous Variants in IFNGR1 Causing Complete IFNGR1 Deficiency. J Clin Immunol. 2024;44(5):111.
21. Filioglou D, Kovacs K, Lafleur BJ, White LM, Katsanis E. Haploidentical Versus Matched Sibling

Donor HCT in Racially Diverse Pediatric and AYA Patients with Hematologic Malignancies: A Single-Center Comparison. Transplant Cell Ther. 2025;31(12):1037 e1- e14.
22. Sedlacek P, Formankova R, Mejstrikova E, Keslova P, Hubacek P, Dobrovolna M, et al. Allogeneic stem cell transplantation in children with leukemia using human leukocyte antigen-mismatched unrelated donors. Pediatr Transplant. 2008;12(1):24-31.
23. Lum SH, Sobh A, Carruthers K, Nademi Z, Watson H, McNaughton P, et al. Improved survival and graft function in ex vivo T-cell depleted haploidentical hematopoietic cell transplantation for primary immunodeficiency. Bone Marrow Transplant. 2021;56(5):1200-4.
24. Slatter M, Lum SH. Personalized hematopoietic stem cell transplantation for inborn errors of immunity. Front Immunol. 2023;14:1162605.
25. Lum SH, Albert MH, Gilbert P, Sirait T, Algeri M, Muratori R, et al. Outcomes of HLA-mismatched HSCT with TCRalphabeta/CD19 depletion or post-HSCT cyclophosphamide for inborn errors of immunity. Blood. 2024;144(5):565-80.
26. Rottman M, Soudais C, Vogt G, Renia L, Emile JF, Decaluwe H, et al. IFN-gamma mediates the rejection of haematopoietic stem cells in IFN-gammaR1-deficient hosts. PLoS Med. 2008;5(1):e26.
27. Thomas-Ruddel D, Giamarellos-Bourboulis E, Neumann C, Briegel J, Roquilly A, Annane D, et al. IFNgamma in human sepsis: a scoping review. Ann Intensive Care. 2025;15(1):112.

Table1. Basic data for patients undergoing transplantation and brief infectious history

Patient No.	Sex	Age of onset	Age at diagnosis	Age at 1st HSCT	IFNGR1 Mutations	IFNGR1 expression level	IFN-γ Level	Infectious history
1	F	1m	2m	9m	c.679dup p.Thr227Asnfs*3	5.6%	high	Disseminated BCG, *A. baumannii*, *P. jirovecii*、*E. faecalis*
2	M	3m	6m	78m	c.655G>A p.G219R	19.8%	normal or slightly elevated	BCG, *N. meningitidis*, *T. marneffei*, *C. parapsilosis*, *S. aureus*, *S. London*
3	F	2m	3m	9m	c.77+5(ivs2)G>C c.188(exon3)C>A	1.7%	slightly elevated	Disseminated BCG, CMV, *R. mucilaginosa*, *C. albicans*

F: female, M: male; *A. baumannii*: *Acinetobacter baumannii, P. jirovecii*: *Pneumocystis jirovecii*, *E. faecalis*: *enterococcus faecalis*, *N. meningitidis*: *Neisseria meningitidis*, *T. marneffei*: *Talaromyces marneffei*, *C. parapsilosis*: *Candida parapsilosis*, *S. aureus*: Staphylococcus aureus, *S. London*: Salmonella London, *R. mucilaginosa*: *Rhodotorula mucilaginosa*, *C. albicans: Candida albicans.*

Table2. Information related to myeloablative conditioning, Graft and donor, and GvHD prophylaxis in HSCT

Patient No.	Infectious status and IFN-γ before HSCT	myeloablative conditioning regimen	Graft	Donor	No. of grafted cells per kg	GvHD prophylaxis
1	No signs of Mycobacterium activity, 9.2 pg/ml	Flu 135mg/m^2, Bu 13.5mg/kg, ATG 7.5mg/kg, TT 10mg/kg	PB-SC	Fully HLA-matched non-relative	13.89×10^8/kg NC 8.21×10^6/kg $CD34^+$	MMF, TAC, MTX
2	No signs of Mycobacterium activity, 20 pg/ml	Flu 170mg/m^2, Bu 13.5mg/kg, ATG 5mg/kg, TT 10mg/k	PB-SC	Half HLA-matched sibling	13.2×10^8/kg NC 10.37×10^6/kg $CD34^+$	MMF, TAC, Cy
3 (1^{st})	CMV infection, ESBL+, No signs of Mycobacterium activity, 122 pg/ml	Flu 120mg/m^2, Bu 13.5mg/kg, ATG 7.5mg/kg	PB-SC	Fully HLA-matched non-relative	8.66×10^8/kg NC 11.8×10^6/kg $CD34^+$	MMF, CsA, MTX
3 (2^{nd})	Good, No signs of Mycobacterium activity, 9.7 pg/ml	Flu 165mg/m^2, Bu 14.5mg/kg, ATG 7.5mg/kg, TT 10mg/kg	PB-SC	8/10 HLA-matched non-relative	13.6×10^8/kg NC 10.2×10^6/kg $CD34^+$	MMF, CsA, MTX

Table 3. Post-HSCT outcomes of three patients with IFNGR1 deficiency

Patient No.	PMN>500	Early Chimerism (+14d~+3m)	Chimerism at last follow up	Acute GvHD /Chronic	Other complications	Outcome and time of follow-up
1	Day13	>99%	>99% (+6months) T cell>99% B cell>99% NK cell>99%	mild cGVHD (eye)	PTLD	Alive, well, >2 years old Only Tacrolimus eye drops
2	Day11	>99%	>99% (Nearly+1year) T cell>99% B cell>99% NK cell>99%	aGvHD(grade II: Skin stage 3) cGvHD: Joint (inactive)	Hemorrhagic cystitis, Arthritis	Alive, well, >8years Successfully drug discontinuance
3 (2^{nd})	Day13	>99%	>99% (+1year) T cell>99% B cell>99% NK cell>99%	None	Pulmonary fungal infection	Alive, well, >4years Successfully drug discontinuance

Table 4: Summary of previously reported successful HSCT in IFNGR1 deficiency

Patient	Age at HSCT	Conditioning regimen	GvHD prophylaxis	Graft	Donor	Acute GvHD (Chronic)	Chimerism (Last test)	Follow-up (after HSCT)	Outcome
1**(12)**	8y	Cy/ATG/TBI	CsA+α-IL2-R antib.	BM	MS	None	Mo 58%, T 61%, B 40%	>6 years	Alive and well
2**(12)**	9y	Bu/Cy	CsA+MTX	BM	MS	Grade II: skin, gut, (+chronic)	Mo 100%, T 100%, B 100%	>6 years	Alive, chronic GvHD resolved
3**(13)**	2y	Bu/Cy	MTX	BM	MS	Skin (+chronic)	Overall 97.5%	2 years	Alive and well
4**(15)**	4y	Bu/Cy	CsA+MTX	BM	MS	None	Overall 97%	13months	Alive and well
5**(16)**	Near2y	Alem/Flu/Bu	TAC+ MMF	CB	5/6UCB	None	My 100%, T 91%	1year	Alive and well
6**(17)**	2y	TT/TREO /Flu/ATG	not provide	BM	MUD	not provide	Complete chimerism	33months	Alive and well
7**(18)**	57y	PT/Bu/Cy	Cy+MMF+ SRL	BM	MS	Grade III: gut	Mo 100%, T 100%, B 100%	20months	Alive, aGvHD resolved
8**(20)**	3y	Bu/Flu	CsA	CB+BM	MS	Skin	My >97%, T 63%, B >97%	1year	Alive, aGvHD resolved

TBI: Total Body Irradiation, Mo: Monocyte, My: myeloid, Alem: alemtuzumab, TREO: Treosulfan, PT: Pentostatin, SRL: Sirolimus.

Figure Legends

Figur1: The process of literature review, N: Number of articles.

Figure

Figure1

