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LETTER TO THE EDITOR

Successful outcome with second hematopoietic stem cell transplantation in a patient with IL-10R deficiency

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Interleukin-10 (IL-10) and IL-10 receptor (IL-10R) deficiencies, which are caused by loss of function mutations in the related genes, are primary immunodeficiencies that result in severe dysregulation of the immune system.[1,2] Patients usually present early in life with an inflammatory bowel disease-like phenotype accompanied with severe perianal disease. Other clinical features of the disease are chronic folliculitis, recurrent respiratory diseases and arthritis.[1–5] Because of poor long-term prospects of the disease, and its resistance to conventional immunosuppressive therapies, allogeneic hematopoietic stem cell transplantation (HSCT) has been performed and proved to be a curative therapeutic approach in several patients.[1,3] Here, we report a child with IL-10R deficiency who underwent second hematopoietic stem cell transplantation using non-myeloablative conditioning regimen due to secondary graft failure.

A 16-month-old boy, the fourth child of consanguineous parents, was admitted to our hospital with recurrent ulceration, abscesses and fissures in the perianal region. He had also chronic diarrhea, malnutrition and growth retardation developed after 2.5 months of age. He was hospitalized several times and underwent surgical interventions for anal fistulas at another center. On admission, his weight was 7500 g (< third percentile), height: 69 cm (< third percentile) and head circumference: 42 cm (< third percentile), and severe anal ulcers were observed. Hemogram showed: hemoglobin 6.2 g/dL, leukocyte 15 900/mm^3 and platelets 231 000/mm^3 with normal absolute neutrophil and lymphocyte numbers. IgA was 214 (30–107), IgG 1720 (605–1430), IgM 316 (66–228) and IgE was 285. Lymphocyte subset analysis showed an increased percentage and number of CD19 positive cells (45% (17–41%) and 3825 cells (600–3100), respectively), and lymphocyte proliferative response was found to be higher than the healthy control. In colonoscopy, deep ulcers, inflammatory polyps and mucosal edema were detected throughout the entire colon. The histopathological analysis of the colon mucosa revealed ulceration, infiltration with mixed inflammatory cells, few cryptitis and destruction of crypts. Molecular analysis showed a homozygous defect in the alpha subunit of IL-10R (c.G477A, p Trp.159X). The patient was treated with anti-inflammatory agents including corticosteroids, mesalazine and azathioprine, however, none of these therapies induced remission or long-term improvement. Broad spectrum antibiotics were administered simultaneously for septicemia and perianal abscess. Nevertheless, the diarrhea was not controlled and he could not gain weight. Hence, parenteral nutrition was started and mesenchymal stem cell therapy was performed in order to control the inflammation before HSCT. This provided a relative improvement in the frequency of diarrhea and consistency of stool.

At the age of 21 months, the patient underwent HSCT from his HLA identical sibling. Characteristics and results of transplantation are shown in Table 1. Parenteral nutrition was given during the peritransplantation period. Diarrhea, abdominal distension and perianal lesions progressively resolved, and weight gain was recorded after engraftment. Chimerism analysis showed 95% donor profile at day +25, but decreased gradually to 54% in the third month and 31% in the fourth month after HSCT. Relapse in the clinical findings, including perianal lesions, diarrhea, feeding intolerance, loss of weight and abdominal distension was observed concurrently in the fifth month of HSCT when the chimerism analysis showed 13% donor profile.

Table 1. Characteristics of patient and results of transplantation

	First HSCT	*Second HSCT*
Age	21 mo	32 mo
Donor characteristics	HLA identical sibling	HLA identical mother
Source of stem cells	BM	PB
The number of nucleated cells (per kg)	5.8×10^8	20.8×10^8
The number of mononuclear cells (per kg)	1.8×10^8	11.7×10^8
The number of $CD34^+$ cells (per kg)	4.6×10^6	9.8×10^6
Conditioning regimen	Bu (16 mg/kg) + Cy (200 mg/kg)	Bu (9.6 mg/kg) + Flu (175 mg/m^2) + ATG (30 mg/kg)
GvHD prophylaxis	CsA+MTX	CsA+MTX
Engraftment	Yes	Yes
Neutrophil engraftment day	+13	+10
Thrombocyte engraftment day	+30	+14
Acute GvHD ($\geqslant$ grade 2)	No	No
Chronic GvHD	No	No
VOD	No	Yes
Hemorrhagic cystitis	No	No
Mucositis ($\geqslant$ grade3)	Yes	No
Neutropenic fever	Yes	Yes
Pulmonary infection	Yes	No
CMV PCR positivity	No	No

Abbreviations: ATG = antithymocyte globulin; BM = bone marrow; Bu = busulfan; CsA = cyclosporine A; Cy = cyclophosphamide; Flu = fludarabine; HSCT = hematopoietic stem cell transplantation; mo = month; MTX = methotrexate; PB = peripheral blood; VOD = venoocclusive disease.

Endoscopic evaluation and biopsies from ileum and colon revealed similar inflammatory changes as previously detected. No clinical response was observed again to multi-immunosuppressive therapy, including corticosteroids, mesalazine and azathioprine.

At the eleventh month after the first HSCT, the patient underwent second HSCT due to secondary graft failure. HLA full-matched mother was chosen as donor this time, and non-myeloablative regimen was preferred for second transplantation. The characteristics and results of transplantation are shown in Table 1. The patient received defibrotide for mild venoocclusive disease in the posttransplant period. Neutrophil and thrombocyte engraftment were detected on day +10 and +14, respectively, and chimerism analysis showed 97% donor profile at +1 month. The patient began to tolerate oral feeding, and gained weight. Chimerism analysis showed 97% donor profile again at +6 months and at 24 months after HSCT. Permanent clinical improvement was seen after the second HSCT. The patient is doing clinically well now at the 29th month of second HSCT.

Current therapeutic strategies in IL-10R deficiency-related inflammatory bowel disease include the use of enteral nutrition, corticosteroids, mesalazine, immunomodulators (azathioprine, 6-mercaptopurine and methotrexate) and anti-TNF-α antibodies. Unfortunately, most of the patients are resistant to these therapies.[3,6] Similarly, the present case did not respond to immunosuppressive treatment. Mesenchymal stem cell treatment which is shown to be effective in the treatment of resistant inflammatory bowel disease,[7] was given to this patient prior to HSCT, to provide, at least, a transient improvement in bowel function and to reduce the risk of transplant-associated complications. To the best of our knowledge, there are six reported cases with IL-10R deficiency underwent HSCT in the literature and favorable outcome was achieved.[1–3,6] First transplantation for IL-10R deficiency in human was reported at 2009 by Glocker *et al.*,[1] and beneficial effects were reported. Kotlarz *et al.*[3] reported the results of five cases (one reported) with IL-10R deficiency who underwent HSCT. Although engraftment was achieved in all patients, one patient developed graft rejection, one patient had mixed chimerism and another had partial bone marrow failure. In this series, the patient who developed graft rejection underwent second HSCT from different donor, which resulted in a prompt and durable engraftment.[3] Likewise, sustained engraftment is achieved in our patient after second HSCT from a different donor. The sixth case treated with HSCT was of Pakistani origin, reported by Engelhardt *et al.* who also achieved engraftment. In addition, remission with HSCT is reported in two patients with IL-10 deficiency.[6]

Highly immunosuppressive and myeloablative conditioning regimens, including alemtuzumab, fludarabine, treosulfan and thiotepa were used for patients with IL-10R deficiency.[1,3] This therapy finds justification in the existing hyperinflammation in IL-10R deficiency in contrast to patients with classical immunodeficiency disorders.[3] In the present case, myeloablative conditioning regimen was preferred in the first transplantation as suggested in the literature; because of the risk of rejection and hyperinflammatory state associated with IL-10R defects. Despite the achievement of early complete donor chimerism, gradual graft rejection occurred. Mixed donor chimerism is increasingly common in HSCT for nonmalignant diseases, especially with the use of reduced-intensity preparative regimen. There are few data about the use of donor lymphocyte infusion (DLI) in this setting in the literature. Haines *et al.*[8] reported the results of a retrospective study in 27 pediatric patients who received DLI for mixed donor chimerism. Although a potential benefit of DLI is shown in this study, no response to DLI is observed in patients with matched sibling donors. It is also reported that 10 patients developed acute GvHD after DLI in this study.[8] We did not use DLI in our patient because of the uncertainty of its benefit and potential risks including acute GvHD and aplasia associated with this approach.

Sustained engraftment and clinical remission is maintained by a non-myeloablative conditioning regimen including busulfan, fludarabine and antithymocyte globulin in the second transplantation. Changing the donor and the stem cell source, and replacing cyclophosphamide with fludarabine in the conditioning regimen may have affected the result of transplantation. In conclusion, HSCT should be considered early in patients with IL-10R deficiency, especially those resistant to immunosuppressive therapy. We think, the use of a non-myeloablative regimen with busulfan and fludarabine may be considered after rejection had occurred using a fully myeloablative regimen in first place in patients with IL-10R deficiency undergoing HSCT. Future studies are required for determination of constituents and type (myeloablative or non-myeloablative) of conditioning regimen.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schäffer AA, Noyan F *et al.* Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009; **361**: 2033–2045.
2 Glocker EO, Frede N, Perro M, Sebire N, Elawad M, Shah N *et al.* Infant colitis—it's in the genes. *Lancet* 2010; **376**: 1272.
3 Kotlarz D, Beier R, Murugan D, Diestelhorst J, Jensen O, Boztug K *et al.* Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology* 2012; **143**: 347–355.
4 Begue B, Verdier J, Rieux-Laucat F, Goulet O, Morali A, Canioni D *et al.* Defective IL10 signaling defining a subgroup of patients with inflammatory bowel disease. *Am J Gastroenterol* 2011; **106**: 1544–1555.
5 Moran CJ, Walters TD, Guo CH, Kugathasan S, Klein C, Turner D *et al.* IL-10R polymorphisms are associated with very-early-onset ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 115–123.
6 Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM *et al.* Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J Allergy Clin Immunol* 2013; **131**: 825–830.
7 Flores AI, Gómez-Gómez GJ, Masedo-González Á, Martínez-Montiel MP. Stem cell therapy in inflammatory bowel disease: a promising therapeutic strategy? *World J Stem Cells* 2015; **7**: 343–351.
8 Haines HL, Bleesing JJ, Davies SM, Hornung L, Jordan MB, Marsh RA *et al.* Outcomes of donor lymphocyte infusion for treatment of mixed donor chimerism after a reduced-intensity preparative regimen for pediatric patients with nonmalignant diseases. *Biol Blood Marrow Transplant* 2015; **21**: 288–292.