VIA MEDICA

SHORT COMMUNICATION

Acta Haematologica Polonica 2024
Number 5, Volume 55, pages 273–275
DOI: 10.5603/ahp.101814
ISSN 0001–5814
e-ISSN 2300–7117

Use of vedolizumab in children with steroid-refractory gastro-intestinal graft-versus-host disease

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Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for a variety of diseases. Graft-versus-host disease (GVHD) is one of the most serious complications after allo-HCT. It is usually classified as either acute or chronic (a/cGVHD) type. Systemic steroid therapy is the first-line treatment in both types of GVHD, but only about half of patients respond to this treatment [1]. A failure of response to standard steroid therapy is defined as: (a) progression within 3–5 days of the start of treatment; (b) an incomplete response within 7–14 days; and/or (C) recurrence of symptoms after reduction of initial dose (known as "steroid dependence") [2]. In such cases, aGVHD treatment can be based on a variety of options, most often including: ruxolitinib, extracorporeal photopheresis (ECP), mycofenolate mofetil (MMF), sirolimus, mesenchymal stromal cells (MSC), anti-thymocyte globulin (ATG), alemtuzumab, daclizumab, infliximab, vedolizumab, methotrexate and rituximab [3].

Vedolizumab is an anti-α4β7 integrin antibody which has been primarily used in the treatment of inflammatory bowel diseases. It has been recently approved for adult patients suffering with steroid-refractory gastro-intestinal (GI) aGVHD [4]. The aim of this paper was to report our preliminary experience of off-label use of vedolizumab in pediatric patients with steroid-refractory GVHD.

Material and methods

In this retrospective report, we analyzed children after allo-HCT who were treated with vedolizumab for steroid-refractory acute GVHD. The patients were recruited since the first use of vedolizumab in our transplant unit in 2022. For this analysis, we included three patients with gastro-intestinal steroid-refractory acute or chronic GVHD (see Tab. I). Vedolizumab was used in patients with severe intestinal GVHD after the failure of first-line therapy. The inclusion criterion for the drug was clinically overt gastrointestinal bleeding or diarrhea in patients with endoscopically confirmed GVHD. The drug was administered off-label on a compassionate use basis to pediatric patients, after obtaining agreement from parents and legal guardians.

Results and discussion

Patient 1

A 7-year-old girl underwent allo-HCT due to myelodysplastic syndrome, refractory anemia (MDS-RCC), and chromosome instability due to Fanconi anemia. She received the graft from an unrelated 9/10 HLA-match female donor.

Conditioning was based on busulfan, fludarabine, cyclophosphamide and anti-thymocyte globulin (ATG). GVHD prophylaxis was performed with cyclosporine and mycophenolate mofetil. The graft contained 2.17×10^8 nucleated marrow cells/kg body weight (bw), including 1.77×10^6 CD34+ cells/kg bw. Filgrastim was administered from the first day after transplantation. On day 5, rituximab was administered as a prophylaxis against EBV reactivation. Letermovir was used for prophylaxis of reactivation of CMV infection. Due to the risk of reactivation of HBV infection, prophylaxis with tenofovir was applied. From day 5 after transplantation, severe abdominal pain and vomiting occurred. On day 7, thickening of the appendix was observed in ultrasound examination, accompanied by low value of serum inflammation indicators. On day 15, laparoscopic appendectomy was performed. Over the following days, hepatic veno-occlusive syndrome (VOD/SOS) was diagnosed, and treatment with defibrotide was initiated.

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Received: 29.07.2024 Accepted: 31.08.2024

At the same time, a cutaneous form of GVHD, stage II, was diagnosed. Steroids were introduced for the treatment, with a good initial response. GVHD skin lesions disappeared after two days. Due to adverse effects, cyclosporine was discontinued on day 31. On day 49, skin aGVHD stage IV was diagnosed (involving c.60% of the skin's surface). Methylprednisolone was used (at a dose of 2 mg/kg bw followed by 5 mg/kg bw due to lack of clinical response), but without significant improvement. Steroid-resistant graft-versus-host disease was diagnosed, and treatment with ruxolitinib was initiated as a second line therapy. Resolution of the skin lesions was observed within a few days, but bleeding occurred from the upper gastrointestinal tract. In endoscopic examination of the gastrointestinal tract, an involvement with GVHD process was revealed in the entire gastrointestinal tract; this finding was confirmed by histopathological results. Progressive three-line cytopenia was observed. The dose of ruxolitinib was reduced, and after the overall condition of the patient had stabilized, vedolizumab was added into therapy. Weekly infusions were administered in a total of four doses (4 × 220 mg). The next two doses were administered one month apart. After reducing the ruxolitinib dose, cutaneous GVHD had exacerbated. Subsequent treatment involved extracorporeal photopheresis (14 two-day cycles in total). During treatment, improvement in stool consistency was observed, but still with little weight gain. We used additionally 10 doses of mesenchymal stem cells (MSC) transfusion. The patient remains in complete remission with no symptoms of gut GVHD, but with moderate symptoms of bronchiolitis obliterans syndrome.

Patient 2

A 7-month-old boy underwent allo-HCT due to severe combined immunodeficiency (SCID T-B+NK–). Hematopoietic cells were transplanted from peripheral blood from a 10/10 HLA match unrelated male donor. Conditioning was performed with fludarabine, treosulfan and ATG. Cyclosporine and mycophenolate mofetil were used for GVHD prophylaxis, and letermovir was administered for anti-CMV prophylaxis. On day 5 after admission, a single dose of rituximab was applied. The early post-transplant period was complicated by a gastrointestinal infection caused by *Stenotrophomonas maltophilia* and dermatitis in the perianal area.

Due to the increasing EBV viral load, pre-emptive treatment for PTLD was implemented. As decreasing donor chimerism was observed, immunosuppressive prophylaxis was reduced, but GVHD of the skin developed. Treatment with methylprednisolone at a dose of 2 mg/kg bw was initiated, with a good initial response in the first four days. However, due to mixed donor chimerism and EBV infection, the dose of methylprednisolone was reduced to 1 mg/kg/bw over the next few days, followed by recurrence of skin GVHD. Steroid therapy had to be increased again. Nevertheless, progression of skin involvement was observed followed by gut GVHD. Clinical symptoms of gastritis and colitis were confirmed in endoscopic and histopathological examination. Stomach, small intestine, cecum, transverse colon and sigmoid colon were confirmed as presenting the pattern of changes typical for cGVHD. MSC and monthly infusions of vedolizumab were additionally used in the treatment. Due to the lack of expected therapeutic effect, ATG was applied again, and the patient's condition began to improve. The administration of vedolizumab and combined immunosuppressive treatment with steroids and cyclosporine was continued. The number of stools gradually decreased, their consistency became solid, and skin lesions disappeared. Intravenous nutrition was discontinued. Due to decreasing donor chimerism, a second bone marrow transplant was performed, but the boy died due to multi-organ complications.

Patient 3

A 16-year-old girl underwent allo-HCT due to AML-M4, with the presence of the KMT2A-AFDN and ITD-FTL3 fusion genes. Conditioning was done with treosulfan, fludarabine, thiotepa and ATG. Hematopoietic cells were obtained from peripheral blood of a HLA-matched unrelated donor; the graft included 6.09×10^8 donor nucleated cells/kg bw, and 7.35×10^6 CD34+ cells/kg bw. GVHD prophylaxis was performed using cyclosporine A and methotrexate on days 1, 3 and 6 after admission. On day 5, a single dose of rituximab was administered for prophylaxis of EBV reactivation. On day 26, the cutaneous form of GVHD was diagnosed at grade III. The treatment included methylprednisolone at a dose of 2 mg/kg bw. The response to steroid treatment was good, with complete resolution of the skin changes on the fifth day of therapy.

However, on day 195, an intestinal GVHD was diagnosed, and systemic steroid therapy was initiated, initially 1 mg/kg bw, then 2 mg/kg bw. Due to a poor response, vedolizumab therapy was started and cyclosporine was shifted to sirolimus. The patient's condition gradually stabilized, her diet was expanded, and parenteral nutrition was reduced. During follow-up gastro- and colonoscopy, macroscopic improvement and a lower intensity of inflammation were observed in histopathological examination. Due to inadequate clinical response, it was decided to continue treatment with vedolizumab. However, the patient suffered from recurrent gastrointestinal infections with dysbacteriosis, and finally died as a result of sepsis and multi-organ failure.

Vedolizumab as a gut-selective immunomodulator has shown good activity in this type of steroid-resistant GI-aGVHD [4–6]. It offers a substantial opportunity for effective therapy in the gastro-intestinal form of GVHD [5, 6]. In our case series, weekly courses of vedolizumab were observed to be safe and effective. GI-GVHD is a risk factor for severe intestinal infections [7], and the risk of clinically severe infection during or after vedolizumab treatment might

Table I. Summary of patient data

Characteristics	Patient 1	Patient 2	Patient 3
Diagnosis	Myelodysplastic syndrome, Fanconi anemia	Severe combined immunodeficiency	Acute myeloid leukemia
Conditioning	Busulfan, fludarabine, cyclophosphamide, ATG	Treosulfan, fludarabine, ATG	Treosulfan, fludarabine, thiotepa, ATG
GVHD prophylaxis	CsA,MMF, tacrolimus	CsA, MMF	CsA, MTX
Treatment of GVHD	Steroids, ruxolitinib, vedolizumab, extracorporeal photopheresis, mesenchymal stromal cells	Steroids, vedolizumab, ruxolitinib, mesenchymal stromal cells	Steroids, vedolizumab
Vedolizumab administration day	77, 84, 91, 98, 106, 134	152, 192, 221, 278	204, 218, 257
Dosage	10 mg/kg bw	10 mg/kg bw	300 mg
Outcome of GVHD treatment	Remission	Remission	Improvement
Outcome	Remission	Death after second HCT (MOF)	Death after sepsis (MOF)

CsA — cyclosporine A; MMF — mycofenolate mofetil; MTX — methotrexate; MOF — multiorgan failure; ATG — anti-thymocyte globulin; GVHD — graft-versus-host disease

be significant [8], although no firm conclusion can be drawn based on such a small group of patients.

In conclusion, our initial experience of the use of vedolizumab in gastro-intestinal a/cGVHD was positive. Further research is necessary to specify the role of vedolizumab in a pediatric setting.

Article information and declarations

Data availability statement

The data that supports the findings of this study is available from the corresponding author upon reasonable request.

Ethics statement

All patients or their parents provided their consent for reporting data related to their treatment.

Authors' contributions

JC, KC — concept and design; investigation and resources; JC — writing; all authors — data curation, critical revision. All authors have read and approved the final version of the manuscript.

Funding

This study was not supported by any funding.

Acknowledgments

The authors thank all nurses for their excellent everyday patient care.

Conflicts of interest

The authors declare no competing interest with respect to this study.

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