Vedolizumab in highly resistant acute gastrointestinal graft-versus-host disease after allogeneic stem cell transplantation: A single-center pediatric series

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Abstract

Background. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a lifesaving procedure in malignant and nonmalignant diseases. However, it is associated with a considerable risk of graft-versus-host disease (GvHD). Steroids are a first-line therapy for acute GvHD (aGvHD), but there is no standard treatment for steroid-resistant (SR) gastrointestinal (GI) aGvHD, which has a poor prognosis. The anti-integrin antibody, vedolizumab, could help in controlling SR GI aGvHD symptoms by blocking lymphocyte extravasation and infiltration of the intestinal wall.

Objectives. To report the outcomes of 3 children with SR GI aGvHD after allo-HSCT, treated with vedolizumab as the last chance drug.

Materials and methods. The study included 3 patients aged from 8 to 10 years who underwent HSCT in Department of Pediatric Bone Marrow Transplantation, Oncology and Hematology at Wroclaw Medical University, Poland, and who developed severe SR GI aGvHD. All patients had grade IV SR aGvHD with GI stage 4 manifestation. Vedolizumab was given as salvage therapy after an ineffective treatment with etanercept, basiliximab, ruxolitinib, extracorporeal photopheresis, and mesenchymal stem cell infusions. Vedolizumab was administered intravenously at a dose of 300 mg.

Results. Only 1 patient achieved GvHD remission and was alive and well 9 months after the discontinuation of the therapy. One child developed a relapse of malignant disease and eventually died, and the third child died of severe aGvHD.

Conclusions. Vedolizumab can be safely used in children with SR GI aGvHD, offering an additional chance for heavily pretreated patients. Prospective pediatric studies on both prophylactic and therapeutic use of the drug are warranted, according to the preliminary results.

Key words: children, hematopoietic stem cell transplantation, graft-versus-host disease, vedolizumab

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Background

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is indicated in a wide range of malignant and nonmalignant diseases. Despite the improvements in human leukocyte antigen (HLA) typing, immunosuppressive therapy and the management of post-transplantation complications, graft-versus-host disease (GvHD) remains a major cause of transplant-associated morbidity and mortality.[1,2] Graft-versus-host disease may develop after allo-HSCT, with the exception of syngeneic transplantations, and the risk is increased in patients receiving a transplant from partially matched donors or peripheral blood stem cells. The manifestations of GvHD are predominantly diagnosed in the gastrointestinal system, skin and liver.[3–5] The staging and grading of GvHD in children are based on the modified Glucksberg classification.[6] The incidence of grade II–IV acute GvHD (aGvHD) in children ranges from 40% to 85% after HSCT from an unrelated donor and approx. 27% when the donor is an HLA-identical sibling.[7–9] Moreover, approx. 70–90% of high-grade (III–IV) aGvHD cases result in preterm mortality.[9,10] Graft-versus-host disease prevention is based on pre- and post-transplantation pharmacological immunosuppression or graft engineering, such as T lymphocyte depletion. The GvHD first-line treatment consists of steroids and calcineurin inhibitors (CNIs),[11] but up to 50% of patients with aGvHD do not respond to this therapy.[12] In steroid-resistant (SR) aGvHD, multiple therapies have been studied, ranging from high-dose steroids to mono- and polyclonal antibodies (basiliximab, daclizumab, etanercept, anti-thymocyte globulin (ATG), infliximab), extracorporeal photopheresis (ECP), or cellular therapies with mesenchymal stem cells (MSCs).[10,13] Steroid-refractory patients have a poor prognosis, and mortality in such patients reaches 80%.[14,15] In this paper, we report the outcomes of 3 children with severe SR gastrointestinal (GI) aGvHD, who were treated with vedolizumab.

Vedolizumab is a humanized monoclonal antibody that inhibits lymphocyte extravasation in the gastrointestinal tract by blocking the interaction between α4β7 integrin and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1).[16] Vedolizumab has been successfully used in the therapy of inflammatory bowel diseases (IBDs). Clinical studies proved the good safety profile of vedolizumab in IBDs.[17]

Objectives

The aim of this study was to report the outcomes of 3 children with SR GI aGvHD after allo-HSCT, treated with vedolizumab as the last chance drug.

Materials and methods

The study included 3 patients aged from 8 to 10 years who underwent HSCT in Department of Pediatric Bone Marrow Transplantation, Oncology and Hematology at Wroclaw Medical University, Poland, and who developed aGvHD. The enrolment criteria included severe multidrug resistant GI aGvHD and an informed consent for the treatment signed by the patient's legal guardians. The GvHD was assessed according to the modified Glucksberg classification.[6] The criteria for SR GvHD were the progression of the disease after 3 days of steroid therapy or a lack of response after 7 days. The SR GvHD therapies were chosen according to the center standards, with anti-cytokine therapies and ECP used as second- and third-line therapies. Further lines of therapy consisted of ruxolitinib or MSC, depending on a physician's choice. The anti-cytokine therapies consisted of etanercept (at a weekly dose of 1 mg/kg body weight (BW)), basiliximab at a weekly dose of 10 mg in children with BW below 20 kg, or 20 mg in patients with BW above 20 kg. Ruxolitinib therapy was initiated at a dose of 5 mg/day and was increased up to 0.15 mg/kg twice a day if no adverse effects were observed. Vedolizumab (Entyvio; Takeda Pharmaceutical Company Ltd., Tokyo, Japan) was administered at a dose of 300 mg in weeks 0, 2 and 6. The treatment overview is presented in Fig. 1.

The ethical approval was waived by the local Ethics Committee of the Wroclaw University Clinical Hospital, Poland, in agreement with the Declaration of Helsinki of 1975.

Results

The characteristics of the patients included in the study are summarized in Table 1. The 1st patient (PT1) was a 9-year-old boy referred for allo-HSCT because of high-risk resistant Burkitt-like non-Hodgkin lymphoma. Pretransplantation conditioning consisted of fractionated total body irradiation (TBI) (at a total dose of 12 Gy), etoposide (at a dose of 60 mg/kg BW) and ATG (at a total dose of 45 mg/kg BW). Cyclosporine A (CsA) on pretransplantation day –1 and methotrexate (MTX) on post-transplantation days +1, +3 and +6, were administered as GvHD prophylaxis. The boy received a peripheral blood stem cell (PBSC) transplant from a 10/10 HLA-matched unrelated donor at a dose of 13.24 7 × 10^6 $CD34^+$ cells per kg of the recipient's BW. In the post-transplantation period, the patient developed grade III/IV mucositis, fever, transplant-associated microangiopathy, and posterior reversible encephalopathy syndrome (PRES). The CsA treatment was stopped and the boy was treated with mycophenolate mofetil (at a dose of 40 mg/kg BW), starting on day +17 after allo-HSCT. The changes in immunosuppressive treatment resulted in the development of aGvHD with skin and gut involvement. Due to steroid resistance, the patient was

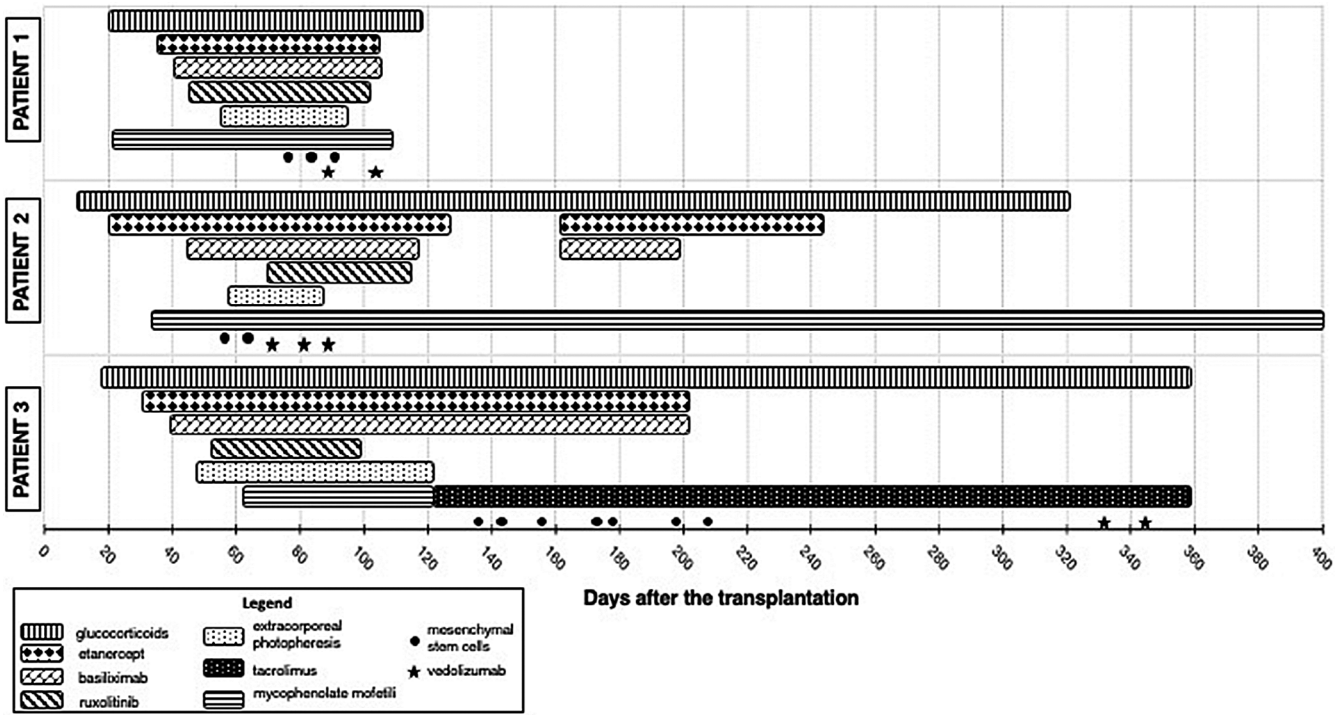

Fig. 1. Immunosupresion therapy overview

Table 1. Patient characteristics

Patients	PT1	PT2	PT3
Diagnosis	Burkitt-like non-Hodgkin lymphoma	chronic myeloid leukemia	acute lymphoblastic leukemia
Age at transplantation [years]	9	8	10
Sex	male	male	male
Type of donor	unrelated	matched sibling (brother)	unrelated
Donor HLA match	10/10	10/10	10/10
Conditioning	TBI 12 Gy, etoposide 60 mg/kg BW, ATG 45 mg/kg BW	fludarabine 4 × 30 mg/m^2, melphalan 140 mg/m^2, thiotepa 2 × 5 mg/kg BW	treosulfan 42 g/m^2, fludarabine 5 × 30 mg/m^2, thiotepa 2 × 5 mg/kg BW, ATG 45 mg/kg BW
Dose of CD34$^+$ cells per recipient kg BW	13.247 × 10^6	3.7 × 10^6	8.07 × 10^6
GvHD prophylaxis	CsA, MTX, MMF	CsA	CsA, MTX
GvHD diagnosis (days after transplantation)	19	11	18
Complications in the post-transplantation period	mucositis grade III/IV, fever, transplant-associated microangiopathy, PRES	CMV reactivation, ADV reactivation	mucositis grade II, fever, hemorrhagic cystitis
Maximum GvHD grade	IV	IV	IV
Maximum GvHD stage (skin/gut/liver)	S3 G4 L0	S4 G4 L1	S4 G4 L0
Number of vedolizumab doses	2	3	2
First dose of vedolizumab [days after transplantation]	88	70	331
Outcome	death of lymphoma	free from GvHD symptoms in 9-month follow-up	death of GvHD

ADV – adenovirus; ATG – anti-thymocyte globulin; BW – body weight; CMV – cytomegalovirus; CsA – cyclosporine A; GI – gastrointestinal; GvHD – graft-versus-host disease; HLA – human leukocyte antigen; MMF – mycophenolate mofetil; MTX – methotrexate; TBI – total body irradiation; PRES – posterior reversible encephalopathy syndrome; PT1 – first patient; PT2 – second patient; PT3 – third patient.

treated with etanercept (from day +34 to day +106 post transplantation), basiliximab (from day +40 to day +106), ruxolitinib (from day +44 to day +100), ECP (from day +55 to day +75), and MSC therapy (on days +76, +84 and +92, each dose 1×10^6 cells per kg of BW). Due to aGvHD progression, at +88 days post transplantation, vedolizumab was started and was administered twice (on days +88 and +102). The aGvHD did not respond to any therapy, and 118 days after HSCT, a relapse of lymphoma was diagnosed. Finally, the boy was transferred to palliative care at home and died of lymphoma progression.

The 2nd patient (PT2) was an 8-year-old boy with chronic myeloid leukemia after allo-HSCT from his 10/10 HLA-matched brother. For pretransplantation conditioning, fludarabine (at a dose of 4×30 mg/m^2), melphalan (at a dose of 140 mg/m^2) and thiotepa (at a dose of 2×5 mg/kg BW) were administered. From pretransplantation day –1, CsA was administered as GvHD prophylaxis. The patient received a bone marrow transplant containing 3.7×10^6 CD34$^+$ cells per kg of BW. Post-transplantation cytomegalovirus (CMV) and adenovirus (ADV) infections required multiple antiviral drugs (ganciclovir, foscarnet, anti-CMV immunoglobulin, brincidofovir, and cidofovir). The aGvHD was reported for the first time at day +11 after transplantation, initially with isolated skin involvement, then progressing to diarrhea and gastrointestinal bleeding. The maximal aGvHD severity was grade IV with skin stage 4, gut stage 4 and liver stage 1. In therapy, etanercept (from day +29 to day +132 post transplantation), basiliximab (from day +25 to day +95), ruxolitinib (from day +53 to day +99), mycophenolate mofetil (at a dose of 40 mg/kg BW, from day +33), ECP (from day +34 to day +68), and MSCs (on days +57 and +64, each dose – 1×10^6 cells per kg BW) were used. The patient achieved the remission of cutaneous symptoms, but no improvement in gastrointestinal manifestation was observed. From day +70, vedolizumab was added, and after 3 doses (on days +70, +82 and +89), a relevant decrease in the stool volume was achieved, with a gradual disappearance of GI aGvHD symptoms. The clinical course at day +97 post transplantation was exacerbated by a massive gastrointestinal bleeding. Gastroscopy and colonoscopy showed massive stomach erosions and lesions throughout the intestinal mucosa. All oral drugs, including ruxolitinib, were stopped, and symptomatic treatment was introduced. The bleeding disappeared completely after 5 days. Subsequently, at day +162, aGvHD flare was diagnosed, with skin grade 3 and gastrointestinal symptoms grade 2/3. The patient responded to therapy with methylprednisolone at a daily dose of 2 mg/kg BW, etanercept and basiliximab. The steroids were tapered after 9 months of therapy, and currently the patient is off immunosuppressive treatment, without any signs or symptoms of GvHD.

The 3rd patient (PT3) was a 10-year-old boy who underwent the transplantation for acute lymphoblastic leukemia (ALL). Pretransplantation conditioning consisted of treosulfan (at a dose of 42 g/m^2), fludarabine (at a dose of 5×30 mg/m^2), thiotepa (at a dose of 2×5 mg/kg BW), and anti-thymocyte globulin (Grafalon, at a total dose of 45 mg/kg BW). The CsA from pretransplantation day –1 and MTX on post-transplantation days +1, +3 and +6 were administered as GvHD prophylaxis. The patient received a transplant from a 9/10 matched unrelated donor, and the grafting material contained 8.07×10^6 CD34$^+$ cells per kg of BW.

The complications that occurred in the post-transplantation period were mucositis grade II, fever, BK virus (BKV)-related hemorrhagic cystitis, and severe aGvHD. From day +18, GvHD skin lesions were reported, classified as skin stage 2, and in the beginning, methylprednisolone (at a dose of 2 mg/kg BW) was administered. The aGvHD progressed to grade IV, due to the presence of diarrhea with severe abdominal pain (gut stage 4) and the appearance of bullae (skin stage 4). The patient was treated with etanercept (from day +28 to day +209 post transplantation), basiliximab (from day +37 to day +209), ECP (from day +45 to day +122), tacrolimus (from day +122), and MSC infusions (days +136, +143, +158, +167, and +179, doses: 1.5×10^6 per kg of BW, and 1.5×10^6 per kg of BW, 1×10^6 per kg of BW, 1×10^6 per kg of BW, 1×10^6 per kg of BW, respectively). The CsA was stopped at day +62 because of angiopathy and replaced with mycophenolate mofetil. From day +122, the basic immunosuppression drug, tacrolimus, was used. From day +185, gastrointestinal GvHD symptoms abruptly escalated, and the flare was treated with methylprednisolone from day +34 to day +68, etanercept and basiliximab from day +195, and MSC infusions on days +199 and +206 (at a dose of 1×10^6 cells per kg of BW). The biopsy of gut mucosa on days +159 and +210 did not reveal typical aGvHD changes. Despite the polytherapy, a clinical response was not obtained. Finally, vedolizumab was introduced and administered twice on days +331 and +345 post transplantation. The general condition of the boy worsened, and GI hemorrhage was observed. Additionally, the symptoms of acute respiratory failure with possible diffuse alveolar hemorrhage were noticed. The boy required mechanical ventilation but died on day +359 after allo-HSCT due to the multiorgan failure.

Discussion

Acute GvHD is one of the most severe complications of HSCT directly associated with treatment-related mortality. The primary role in the pathogenesis of GvHD is the cytokine storm caused by tissue damage, and the ensuing activation of alloreactive donor T lymphocytes that infiltrate and damage host tissues.[18] During the initiation and infiltration phases, targeting the immune system with different immunosuppressants is a cornerstone of a successful therapy. The multidirectional therapy can be seen as a way of interrupting the vicious cycle of uncontrolled

immune system activation, but optimal combinations and drug administration sequences have never been studied in randomized clinical trials. Most clinical evidence on aGvHD therapy is based on small, typically retrospective studies. Among the different mechanisms that can be targeted with drugs modifying the reactivity of the immune system, T-cell trafficking is a relatively new area that has been studied in IBDs.

For the GI aGvHD pathomechanism, the expression of α4β7 integrin on donor T lymphocytes, which mediates lymphocyte trafficking to intestinal tissue, is essential.[16,19] An α4β7 integrin is a cell surface adhesion molecule that mediates the selective adhesion of lymphocytes to MAdCAM-1 or vascular cell adhesion molecule-1 (VCAM-1).[20,21] Different studies have shown that the expression of α4β7 molecules on both memory $CD4^+$ and $CD8^+$ T cells is correlated with the development of GI aGvHD, and is significantly higher than in patients with acute skin GvHD or without GvHD.[16,19,22,23] Gut-selective properties distinguish vedolizumab from other immunosuppressive drugs, and, as shown by Wyant et al., vedolizumab reduces only the immune response to antigens administered orally (oral cholera vaccine), but does not affect the response to substances administered parenterally (such as intramuscular hepatitis B vaccine).[24] Most likely, due to vedolizumab gut selectivity, the risk of opportunistic infections is tolerable and estimated at 0.85% incidents per patient per year. There are no reports on the increased risk of malignancy incidence or recurrence. Adverse events after vedolizumab infusion were noted in less than 15% of patients, and most effects were categorized as minor and reversible, including otitis externa and periorbital edema, intractable itch, shortness of breath during the 4th infusion, upper respiratory tract infections, nausea, fatigue, headaches, nasopharyngitis, and skin infections.[25,26]

In the literature, there are few reports on the successful use of vedolizumab in diseases such as IBD,[26] immune checkpoint inhibitor-induced enterocolitis and GI aGvHD.[27–30] The efficiency of this therapy in aGvHD is not clear. According to Norwegian researchers, in 6 patients with SR GI aGvHD treated with vedolizumab, a clinical response was observed, and there were 4 survivors at a median follow-up of 10 months.[31] Another group presented the results in 6 patients who received vedolizumab as a third- or fourth-line therapy for SR GI aGvHD, 5 of whom died at a median of 32 days (range: 7–172 days) of follow-up.[32] Likewise, Coltoff et al. reported 9 patients with SR GI aGvHD treated with vedolizumab who responded within 10 days after receiving the 1st dose, but only one patient was alive at 100 days after drug administration.[28]

Most responses were observed 7–10 days after vedolizumab administration.[27,28,31]

Early initiation of vedolizumab was more effective than in more advanced therapy lines. According to Danylesko et al., vedolizumab used as second-line therapy showed a conversion rate (CR) of 54% compared to 6.25% in patients treated with the drug in later rounds of treatment.[27]

The GvHD therapy after allo-HSCT is associated with a high risk of opportunistic infections but in our group, no serious infection attributable to vedolizumab was observed. Multicenter studies with patients treated with vedolizumab for IBD or aGvHD estimated the risk of infectious complications in 26% of patients in such populations.[26,27,29] These risks are significantly higher in anticytokine therapies in SR aGvHD (83–100% for infliximab and 67% for etanercept).[33–35] In the case of allo-HSCT recipients treated with intensive immunosuppression, the issue of diminishing the graft-versus-malignancy effect and an increased relapse risk must be considered.[36] In the literature, the incidence of malignancy recurrence was 10%, which is similar to that in patients treated with other anti-GvHD drugs.[13,37,38] In our group, the relapse was detected in 1 child, but it could not be directly attributed to the immunosuppressive therapy.

Interestingly, the role of vedolizumab in the prevention of GvHD was studied, in addition to standard prophylaxis. The drug was administered at a dose of 300 mg on days +21, +113 and +142, and no grade III–IV GI aGvHD was observed, although this needs further study.[39]

Limitations

The main limitation of our research is a relatively small sample of patients. Moreover, it was a retrospective study. Multicenter cohort studies are needed to demonstrate the efficacy of vedulizumab in the treatment of SR GI aGvHD.

Conclusions

In summary, vedolizumab is one of the new therapeutic options in aGvHD. Vedolizumab can be safely used in children with an additional chance of response, even in heavily pretreated patients. Prospective pediatric studies both in prophylaxis and therapy are warranted according to the available results.

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