Vedolizumab therapy for pediatric steroid-refractory gastrointestinal acute graft-versus-host disease

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April 05, 2024

Abstract

Vedolizumab is an immunosuppressive drug that acts locally on the gastrointestinal tract, is mainly used for the treatment of inflammatory bowel disease, and has been reported to be effective against gastrointestinal acute graft-versus-host disease (GI-aGVHD) in adults. However, there is insufficient evidence for pediatric GI-aGVHD. We used vedolizumab in three cases of GI-aGVHD aged 1.5-4.4 years. It was significantly effective in two cases and all cases had no serious side effects. Vedolizumab might be effective and safe for pediatric GI-aGVHD refractory to other treatments. Future study awaits.

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Word count

Main text: 1196 words, Abstract: 87 words

The number of tables and figures: two figures and one supplemental table

Short running title: Vedolizumab for refractory GVHD

Keywords: vedolizumab, GVHD, children, gastrointestinal tract, refractory

Abbreviations key

aGVHD	acute graft-versus-host disease
GI	gastrointestinal
TNF	tumor necrosis factor
IBD	inflammatory bowel disease
BMT	bone marrow transplantation
MTX	methotrexate
TBI	total body irradiation
ATG	anti-thymocyte globulin
mPSL	methylprednisolone
NF-κB	nuclear factor-κB
NEMO	NF-κB essential modulator
PSL	prednisolone
BUD	budesonide
SCN	severe congenital neutropenia
MMF	mycophenolate mofetil

Abstract

Vedolizumab is an immunosuppressive drug that acts locally on the gastrointestinal tract, is mainly used for the treatment of inflammatory bowel disease, and has been reported to be effective against gastrointestinal acute graft-versus-host disease (GI-aGVHD) in adults. However, there is insufficient evidence for pediatric GI-aGVHD. We used vedolizumab in three cases of GI-aGVHD aged 1.5-4.4 years. It was significantly effective in two cases and all cases had no serious side effects. Vedolizumab might be effective and safe for pediatric GI-aGVHD refractory to other treatments. Future study awaits.

Introduction

Acute graft-versus-host disease (aGVHD) is one of the most important complications after allogeneic hematopoietic cell transplantation. Steroids are the first option to treat aGVHD, but gastrointestinal acute GVHD (GI-aGVHD) is often refractory to steroids, compared with skin aGVHD. The efficacy of second-line treatments, such as TNFα inhibitors and mesenchymal stem cells, remain insufficient.

Vedolizumab is a monoclonal antibody that inhibits migration of T lymphocytes into the digestive tract by targeting α4β7 integrin, which is expressed on the activated T lymphocytes and binds to the homing receptor specifically expressed in mesenteric lymph nodes and Peyer's patches. Vedolizumab has shown high response rates and safety for steroid-refractory inflammatory bowel disease (IBD)[1,2], and is approved by the Food and Drug Administration. Considering its mechanism of action, vedolizumab is also expected to be effective against GI-aGVHD without systemic immunosuppression. Previous reports suggested effectiveness of vedolizumab against GI-aGVHD. However, vedolizumab treatment for aGVHD is still limited to case reports and small case series, particularly for children. Here we describe three pediatric GI-aGVHD cases in which vedolizumab was effective and safe.

Cases

Patient 1 was a 3-year-old boy who underwent bone marrow transplantation (BMT) for chronic granulomatous disease from an 8/8 HLA-matched unrelated donor. A second BMT was performed due to secondary graft failure at the age of 4.4 years from another HLA-matched unrelated donor, with tacrolimus and methotrexate (MTX) for GVHD prophylaxis. The conditioning regimen included 3 Gy of total body

irradiation (TBI), fludarabine, busulfan, and anti-thymocyte globulin (ATG) at 5 mg/kg. At day 26 after transplantation, he developed skin rash and diarrhea and aGVHD grade II (skin stage 2, GI stage 1) was diagnosed, which was confirmed by gastrointestinal endoscopy findings. Methylprednisolone (mPSL) 1 mg/kg/day was initiated from day 32, but aGVHD worsened to grade III (skin stage 3, GI stage 3) on day 40. The mPSL was increased to 2 mg/kg/day and human mesenchymal stem cells were administered. The skin rash resolved, although the GI-aGVHD still did not improve. Based on pathological findings compatible with aGVHD, we commenced vedolizumab at 177 mg/m^2/dose intravenously for an hour from day 100. From day 113, the stool form improved and frequency decreased to 1-3 times per day. Vedolizumab was administered 2 weeks and 6 weeks after the initial administration, and was repeated every 8 weeks thereafter. The mPSL was tapered and successfully discontinued on day 759. No adverse event related to vedolizumab was observed.

Patient 2 was a boy with diagnosed nuclear factor-κB (NF-κB) essential modulator (NEMO) deficiency at 6 months. He received BMT from an HLA-mismatched unrelated donor at 1.5 years old, with tacrolimus and MTX for GVHD prophylaxis. The conditioning regimen included fludarabine, busulfan, and ATG at 5 mg/kg. At day 132, he presented with diarrhea and GI-aGVHD was diagnosed based on endoscopic findings. Prednisolone (PSL) 0.5 mg/kg/day, weekly MTX, and enteric-coated budesonide (BUD) were administered, but the effect was insufficient and diarrhea recurred when PSL was tapered. At day 183, he had bloody stools. GI-aGVHD stage 4 was diagnosed and we started vedolizumab 177 mg/m^2/dose intravenously for two to three hours, from day 205. One week after the administration of vedolizumab, the second dose was postponed due to suspected enteritis suggested by elevation of serum C-reactive protein and an abdominal X-ray showing a dilated intestinal tract. Cytomegalovirus enteritis was pathologically negative, with no evidence of bacterial infection, and CRP decreased spontaneously. Treatment was resumed from day 231, but was not sufficiently effective. PSL could not be tapered. At day 314, secondary graft failure was diagnosed, and a second BMT from an HLA haploidentical father was performed with post-transplant cyclophosphamide. Engraftment was successfully achieved, and currently, two months after the second transplantation, he is alive without GI-aGVHD.

Patient 3 was a girl who received BMT from an HLA-mismatched unrelated donor for severe congenital neutropenia (SCN) at the age of 1 year and 9 months. GVHD prophylaxis was performed with tacrolimus and MTX. Conditioning included 3 Gy of TBI, fludarabine, cyclophosphamide, melphalan, and ATG at 10 mg/kg. At day 188, she presented with diarrhea and GI-aGVHD was diagnosed by endoscopy. PSL of 1 mg/kg/day, weekly MTX, and BUD were not effective. Following this, mPSL pulse (30 mg/kg/day), PSL 2 mg/kg/day, mycophenolate mofetil (MMF), cyclosporine, and infliximab were administered, but GI-aGVHD still remained and she was dependent on parenteral nutrition. Vedolizumab was started from day 274 at the same dose as patient 2, and repeated after 2 and 6 weeks, and every 8 weeks thereafter. Diarrhea improved immediately and colonoscopic findings also significantly improved after the second and seventh dose of vedolizumab (Fig. 2). MMF and steroids were successfully terminated at day 330, with neither GVHD recurrence nor adverse events related to vedolizumab.

Discussion

In the previous reports of vedolizumab for adult GI-aGVHD patients, the median time to the initial response was 10-22 days and the overall response rate for steroid-refractory GI-aGVHD was 64%-79%.[3,4] In our cases, response was achieved in two of three cases and the time to the initial response was 10 days and 13 days, respectively. Vedolizumab showed prompt response and was thought to be potentially effective in children with even heavily treated and refractory GI-aGVHD.

Early treatment with vedolizumab may lead to better therapeutic response. Danylesko *et al* reported that 54% of patients receiving vedolizumab as second-line therapy achieved CR, compared to 6.25% in patients administered vedolizumab as third-line and later.[4] In our cohort, unlike the previous report, patient 2 did not respond to vedolizumab as second line treatment, whereas patients 1 and 3 received vedolizumab as third-line or later and obtained a good response. Further studies are required to identify biomarkers which predict efficacy of vedolizumab for GVHD.

In the report of Fløisand *et al* , serious adverse events were observed in 15 of 29 cases, about half of which were infections[3], although our three cases fortunately did not suffer any severe adverse events related to vedolizumab. Vedolizumab acts specifically against activated T cells destined for the lower digestive tract, so systemic immunosuppression hardly occurs.[5] As other systemic immunosuppressants are considered to be risk factors for infections, we believed that it would be desirable to administer vedolizumab earlier.

As for previous pediatric experience with vedolizumab for GVHD, only six cases were reported.[6,7] None of the patients experienced severe complications and, of the three evaluable cases, two cases had complete response. Although our cases were younger than these cases (1.5 - 4.4 years vs 6 - 15 years), vedolizumab was similarly safe and effective. In pediatric cases other than GVHD, a report of 12 cases with vedolizumab against IBD showed that vedolizumab was effective in children as well as in adults, and there was only one serious adverse event of a systemic allergic reaction.[8] Although no child-specific adverse events related to vedolizumab administration have been published to date, the observation period is still short. Further large-scale prospective studies are desired to confirm the efficacy and safety of vedolizumab for GVHD in children.

In conclusion, our experience suggests a potential efficacy and feasibility of vedolizumab for refractory GI-aGVHD in children. Further cases should be accumulated.

Acknowledgements

The authors would like to thank the physicians in the Department of Pediatrics, Hiroshima University for the management of patient 3. The authors thank the medical editor from the Division of Postgraduate Education and Training at the National Center for Child Health and Development for professionally editing this manuscript.

This study is funded in part by a research grant from the National Center for Child Health and Development (2020A-1).

Conflict of interest

All authors declare no conflicts of interest.

Author contributions

M.K. and H.K. designed the research; K.I., T.K., A.E., K.O., T.O., T.K., K.A., D.T., K.O., M.N., and K.I. collected data; K.I., T.K., M.K., and H.K. drafted the paper; all authors discussed the results and commented on the manuscript.

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Figure legends

Figure 1. Treatment course of gastrointestinal aGVHD.

A, Patient 1: aGVHD was refractory to hMSC but responded well to vedolizumab. B, Patient 2: aGVHD was difficult to treat even after administration of vedolizumab. He underwent a second BMT due to secondary graft failure. C, Patient 3: aGVHD was refractory to mPSL pulse and infliximab, but improved after administration of vedolizumab.

hMSC, human mesenchymal stem cells; BMT, bone marrow transplantation; mPSL, methylprednisolone.

Figure 2. Endoscopic improvement by vedolizumab.

Representative endoscopic images in patient 3. The images of ileum (C, D, F, G and H), ileocecal valve (I), ascending colon (E), descending colon (B), and sigmoid colon (A) are shown. Before vedolizumab, aphthous erosions had spread to the entire colon and some had longitudinal ulcers (A, B, and C). Before vedolizumab, aphthous erosions had spread to the entire colon and some had longitudinal ulcers (A, B, and C). After the second dose of vedolizumab (D, E, and F), erosions were significantly improved and the ulcers were scarred or accompanied by regenerative epithelium. After the seventh dose of vedolizumab (G, H, and I), colonic mucosa was almost normal except for one scar on the side of the ileocecal valve.