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Safety and Effectiveness of Vedolizumab in Patients with Steroid-Refractory Gastrointestinal Acute Graft-versus-Host Disease: A Retrospective Record Review

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A B S T R A C T

Allogeneic hematopoietic cell transplantation (allo-HCT) can be curative in patients with hematologic malignancies but carries a significant risk of graft-versus-host disease (GVHD). There are no standard treatments for steroid-refractory (SR) gastrointestinal (GI) acute GVHD (aGVHD). This multicenter, international, retrospective medical record review aimed to evaluate the off-label use of vedolizumab, a gut-selective immunomodulator, for treating SR GI aGVHD. Data were collected from patients' medical records; criteria for extraction included no more than 1 allo-HCT and at least 1 dose of vedolizumab as treatment for SR GI aGVHD (ie, stage 1 to 4 GI aGVHD following ≥1 previous treatment regimen(s) containing ≥1 mg/kg methylprednisolone or equivalent). Descriptive analyses of response rate, overall survival (OS), and serious adverse effects (SAEs) were performed. Twenty-nine patients were identified from 7 sites who had received 1 to 10 doses of vedolizumab 300 mg i.v. (median 3 doses) as treatment for SR GI aGVHD. The overall response rate at 6 to 10 weeks after vedolizumab initiation was 64%, and OS at 6 months was 54%. There were 29 SAEs, including 12 infections; 3 SAEs were considered possibly related to vedolizumab, 2 of which were infections. Thirteen SAEs were fatal, 1 of which was possibly vedolizumab-related. There were 8 nonserious infections and 1 serious infection with confirmed GI origin in 8 patients; there was no apparent pattern in the timing of these infections relative to the initiation of vedolizumab treatment. Further data on the efficacy and safety of vedolizumab in this setting from prospective trials are needed.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) can be curative in patients with hematologic malignancies or benign hematologic conditions, but its success is limited by the development of graft-versus-host disease (GVHD) [1,2]. Acute GVHD (aGVHD) most commonly involves the skin, liver, and gastrointestinal (GI) tract [3,4]. aGVHD of grade II-IV and grade III-IV have been reported in 39% to 71% and 14% to 32% of allo-HCT recipients, respectively, even with standard methods of GVHD prophylaxis [5,6]. Skin is the most commonly affected organ [7], but up to 60% of patients have GI involvement, which may result in persistent anorexia, secretory diarrhea, abdominal pain, and/or hemorrhage [8]. A study of 1462 patients who underwent allo-HCT between January 2000 and December 2005 found that 8% of patients developed stage 3 or 4 GI aGVHD and had an overall survival (OS) of 25% at 2 years [9]. Other studies have demonstrated that grade III-IV aGVHD with GI tract involvement is associated with very high overall mortality (70% to 90%) [6].

Treatment options for patients with aGVHD are limited. Corticosteroid therapy is most often used as first-line treatment in patients with grade II or higher aGVHD; however, this is

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effective in <50% of patients, and only one-third achieve a durable remission with corticosteroids alone [10]. Patients with lower GI involvement are typically less responsive to therapy and have higher morbidity and mortality than those without lower GI involvement [11]. For patients who develop steroid-refractory (SR) aGVHD, there currently are no proven standard salvage therapies approved by the US Food and Drug Administration or the European Medicines Agency. Several therapies used historically have been assessed as off-label, second-line treatment options, including the chemotherapeutic drug pentostatin [12], antithymocyte globulin (ATG) [13], and monoclonal antibodies including alemtuzumab [14], infliximab [15], and basiliximab/infliximab combination therapy [16]. More recently, ruxolitinib and tocilizumab have been investigated [17-19], and a phase I trial of brentuximab vedotin has been conducted [20]. However, clinical outcomes for patients receiving these therapies are poor, with morbidity and mortality remaining high, and thus there is an unmet need for efficacious therapies for SR aGVHD with acceptable safety profiles [21,22].

Key to the pathogenesis of GI aGVHD is the expression of the $\alpha_4\beta_7$ integrin on immunocompetent donor T lymphocytes that migrate to lymphoid tissues soon after infusion and become activated on interaction with host antigen-presenting cells in the GI tract [23,24]. Vedolizumab is a monoclonal antibody directed against $\alpha_4\beta_7$ integrin, which mediates migration of lymphocytes to the GI mucosa and gut-associated lymphoid tissue. Vedolizumab is currently approved for the treatment of inflammatory bowel diseases [25,26]. By inhibiting $\alpha_4\beta_7$ integrin, vedolizumab may interfere with gut-selective T lymphocyte trafficking, and it may be a treatment option for patients with SR GI aGVHD. This has led some clinicians to use vedolizumab off-label in these patients, and published case series have suggested clinical activity in patients with GI aGVHD [27-30]. The aims of this international, retrospective record review were to further evaluate the real-world use of vedolizumab in the off-label setting for treating patients with SR GI aGVHD, and also to assess key clinical outcomes in these patients, including those related to the safety and effectiveness of vedolizumab therapy.

METHODS

Takeda Pharmaceutical Company receives retrospective reports of patients receiving commercial vedolizumab for the treatment of SR GI aGVHD. Although Takeda had no influence on physicians' use of vedolizumab to treat these patients, this retrospective record review study was conducted by contacting those centers providing reports to improve understanding of the real-world clinical outcomes of vedolizumab in the off-label setting.

This observational, retrospective record review involved 7 international sites in Belgium (n = 2), Norway (n = 1), Sweden (n = 2), and the United States (n = 2) in which 2 or more patients had received vedolizumab as off-label treatment for SR GI aGVHD between January 2015 and March 2017. The local Institutional Review Board at each center approved the study, and written consent was received where required by an independent Ethics Committee. Routinely collected data from the medical records of eligible patients at participating sites at the time of study initiation were extracted and entered into an electronic case report form by a participating physician or a trained data abstractor. Data concerning patients' clinical history and treatment before and after initiation of vedolizumab were extracted as well.

Eligibility of Patients

To be eligible for data extraction, adult patients must have undergone only 1 allo-HCT and received at least 1 dose of vedolizumab 300 mg i.v. as treatment for SR GI aGVHD, which was defined as active stage 1 to 4 GI aGVHD following at least 1 previous treatment regimen containing at least 1 mg/kg methylprednisolone or equivalent daily dose for GI aGVHD. No further details regarding SR status were required for patient eligibility and subsequent data extraction of medical records, but GI aGVHD was confirmed as SR by the treatment providers at each center. Thus, all patients received vedolizumab as a second-line or later-line therapy.

Diagnosis of GI aGVHD was made by the treatment providers and confirmed by biopsy for most patients. Patients were eligible for data extraction regardless of donor source, conditioning regimen intensity, and previous GVHD prophylaxis received. Data on additional therapies for aGVHD after vedolizumab were not extracted.

Treatment and Evaluation of Response

In patients eligible for data extraction, vedolizumab was administered at the same dose and schedule approved for the treatment of inflammatory bowel disease [25,26]: an initial dose of vedolizumab 300 mg i.v. at week 0, followed by the same dose at weeks 2 and 6 and then every 8 weeks thereafter. Continuation of treatment in patients with SR GI aGVHD after each dose was dependent on patient response and functional status, disease status at the time of the scheduled infusion, and the discretion of the treating provider.

When available, the following data were collected from the medical records of eligible patients (no imputation of values for missing data was performed): patient and disease characteristics; donor-transplant type; conditioning and GVHD prophylaxis; post-transplantation complications before vedolizumab treatment; details on the outcome of allo-HCT; previous treatments received for aGVHD; aGVHD clinical staging, grading, and assessment of response in all organs; and aGVHD and disease outcomes, including OS and serious adverse effects (SAEs).

During extraction of the relevant data, the clinical stage and severity of aGVHD were defined according to the modified Glucksberg criteria [31]. Response to vedolizumab was categorized as complete response (CR), very good partial response (VGPR), partial response (PR), or no response. Data on disease progression and death were also extracted. Data for response were not extracted for this analysis when a patient's information was insufficient to distinguish between PR and VGPR. CR was defined as resolution of all signs and symptoms of aGVHD. VGPR was defined as specific improvement in skin manifestations, liver involvement, and GI tract involvement, according to the criteria described by Martin et al [32]. PR was defined as an improvement of 1 aGVHD stage in at least 1 organ without progression in any other organs.

SAEs

Consistent with standard definitions, SAEs recorded in patients' medical records were classified by physicians and defined as any untoward medical occurrence at any dose that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly/birth defect, or was a medically important effect that might not fit within the foregoing criteria but was considered serious based on appropriate medical judgment. All SAEs that were recorded from the first dose of vedolizumab through to 18 weeks after the last dose of vedolizumab were extracted; after this time, only SAEs considered related to vedolizumab treatment were extracted. This 18-week limit was selected because it is approximately 5 half-lives after the last dose of vedolizumab (using a half-life of vedolizumab 300 mg in patients with inflammatory bowel disease of approximately 25 days) [33]. An adverse effect was considered related to vedolizumab if the investigator responded yes to the following question: "Is there a reasonable possibility that the adverse effect is associated with the study drug?"

Analyses

Descriptive epidemiologic analyses were performed on the extracted data to assess the SR GI aGVHD response rate following vedolizumab treatment, OS up to 12 months, and SAEs. A Kaplan-Meier plot for OS was generated.

RESULTS

Missing Data

No imputation of missing values was performed, meaning that extracted data were limited to those routinely collected in the electronic medical record. Data not available for all patients included the end date of treatments received during vedolizumab therapy, treatments received after the final dose of vedolizumab, disease risk index at the time of allo-HCT, response rates at certain follow-up times, and the origin of all infections.

Patient Characteristics

A total of 29 patients who met the eligibility criteria for data extraction were identified, with a median age of 50 years (range, 19 to 69 years) (Table 1). The most common indication for transplantation was acute myelogenous leukemia or a related precursor neoplasm (28%) (Table 1). Nine patients (31%) received a myeloablative condition regimen, and 20 (69%) received a nonmyeloablative or reduced-intensity conditioning regimen. During the study period for which data were

Table 1
Patient Characteristics at the Time of Allo-HCT (N = 29)

Characteristic		Value
Age, yr		
Mean (SD)		48.0 (15.3)
Median (range) (IQR)		50 (19-69) (37-59)
Female sex, n (%)		7 (24)
Primary disease indication for allo-HCT, n (%)		
	AML or related precursor neoplasm	8 (28)
	Mature B lymphocyte neoplasm	3 (10)
	Myelodysplastic syndrome	3 (10)
	Precursor lymphoid neoplasm	3 (10)
	Myelodysplastic/myeloproliferative neoplasm	2 (7)
	Mature T lymphocyte and NK cell neoplasm	1 (3)
	Myeloproliferative neoplasm	1 (3)
	Other*	8 (28)
Disease control, n (%)		
	CR	17 (59)
	PR	12 (41)
Disease Risk Index [47,48], n (%)		
	Low	4 (14)
	Intermediate	9 (31)
	High	6 (21)
	Very high	0 (0)
Conditioning regimen, n (%)		
	Myeloablative	9 (31)
	Nonmyeloablative or reduced-intensity	20 (69)
Donor relationship, n (%)		
	Related donor	7 (24)
	Unrelated donor	22 (76)
Source of donor cells, n (%)		
	Bone marrow	5 (17)
	Mobilized peripheral stem cells	24 (83)
Duration of treatment with corticosteroids before the first dose of vedolizumab, d, median (range)		15 (1-236)
Duration from diagnosis of aGVHD to first dose of vedolizumab, d, median (range)		14 (2-147)
aGVHD grade at initial diagnosis, n (%)		
	III	26 (90)
	IV	3 (10)
Gastrointestinal aGVHD stage at the initial dose of vedolizumab, n (%)		
	0	0 (0)
	1	5 (17)
	2	6 (21)
	3	11 (38)
	4	7 (24)

AML, acute myelogenous leukemia; CMML, chronic myelomonocytic leukemia; IQR, interquartile range; MF, myelofibrosis; NK, natural killer; SD, standard deviation.
* Aplastic anemia, chronic lymphocytic leukemia, CMML converted to AML, CMML/MF, multiple myeloma, and very severe aplastic anemia in 1 patient each, and Hodgkin disease in 2 patients.

evaluated, 3 patients experienced relapse of their primary malignancy; all of these patients died, at 420, 288, and 94 days after the date of initiation of vedolizumab (Figure 1).

The median time to initial diagnosis of aGVHD from allo-HCT was 36 days (range, 20 to 131 days). At initial diagnosis, all patients had grade III-IV aGVHD (90% with grade III and 10% with grade IV); at vedolizumab initiation, 28 patients (97%) had stage 2 to 4 GI involvement, and 1 patient (3%) had stage 1 involvement. The median interval between aGVHD diagnosis and the initial dose of vedolizumab was 14 days (range, 2 to 147 days), and the median duration of treatment with corticosteroids before this initial dose was 15 days (range, 1 to 236 days) (Table 1). Consistent with the eligibility criteria for data extraction, all 29 patients had GI tract involvement at initiation of vedolizumab treatment; 8 also had liver involvement, and 12 also had skin involvement. Patients received 1 to 10 (median, 3) doses of vedolizumab 300 mg i.v. as treatment for SR GI aGVHD following the schedule approved for inflammatory bowel disease. Six of the 29 patients received only 1 dose of vedolizumab (Figure 1).

Therapies Received before or during Vedolizumab Treatment

All patients had received corticosteroids as first-line treatment before initiation of vedolizumab therapy, meaning all patients were treated with vedolizumab in the second- or later-line setting. Of the aGVHD treatments reported, the most common therapies other than corticosteroids were mycophenolate mofetil (n = 8), calcineurin inhibitors (n = 7), extracorporeal photopheresis, and ruxolitinib (n = 5 each) (Table 2).

Treatment Response and OS

The median time to the initial reported response from the first dose of vedolizumab was 22 days (range, 7 to 73 days) (Figure 1). At assessments made 6 to 10 weeks after initiation of vedolizumab (8 weeks of follow-up), data on 25 patients

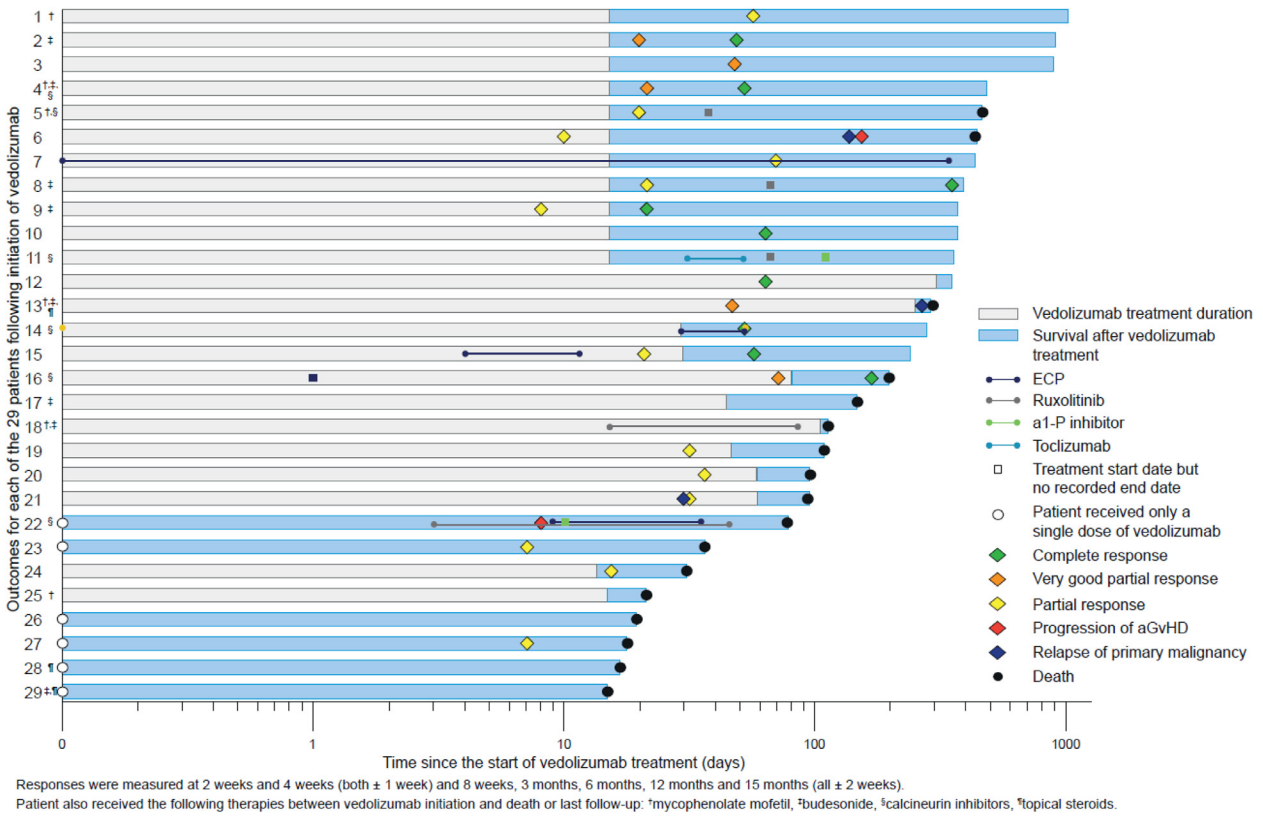

Figure 1. Swimmers plot of therapies received during vedolizumab treatment and patient outcomes following initiation of vedolizumab treatment (n = 29). Each line represents 1 of the 29 patients analyzed, ordered by duration of survival after initiation of vedolizumab treatment (from the longest to the shortest number of days). The 6 patients receiving only a single dose of vedolizumab are denoted with a white filled circle on the *y*-axis. Responses to vedolizumab (CR, VGPR, and PR) are displayed as colored diamonds, as are the 3 relapses of primary malignancy and each occurrence of disease progression observed during the study period. Patients who died before the final follow-up are indicated with a solid black circle at the end of their respective line. Other therapies for aGVHD received during vedolizumab therapy are indicated by thin colored lines, or colored squares if the treatment had no recorded end date. Overall response was defined as PR or better (including PR, VGPR, and CR). A1-P, alpha-1 antitrypsin; ECP, extracorporeal photopheresis.

(86%) were evaluated for response to treatment (Table 3). The overall response rate (CR, VGPR, or PR) to vedolizumab in these patients was 64% (16 of 25); the corresponding rates for CR, VGPR, and PR were 28% (7 of 25), 24% (6 of 25), and 12% (3 of 25), respectively. At 8 weeks after the first dose of vedolizumab, 12% of patients (3 of 25) had experienced no response to treatment, and 24% (6 of 25) had died. The causes of death before 8 weeks of follow-up were infection and aGVHD, multiorgan failure, pulmonary hemorrhage and multiorgan failure, progression of aGVHD, sepsis, and aspiration pneumonia and sepsis.

OS at 6 and 12 months after the first dose of vedolizumab was 54% and 47%, respectively (Figure 2).

SAEs

There were 29 SAEs recorded in 15 patients after the initiation of treatment with vedolizumab up to either death or the date of last follow-up (Table 4). Of these 29 SAEs, 12 were infections, 4 were GI-related, 4 were hematologic, 2 were cardiovascular, 2 were respiratory, 2 involved the central nervous system, 1 was psychological, 1 was multiple organ failure, and 1 was renal.

In total, 3 SAEs were considered possibly related to vedolizumab treatment, including 2 infections: grade 3 CMV colitis, which resolved, and grade 4 sepsis, which had a fatal outcome. The third possibly treatment-related SAE was grade 4 GI-related bleeding from the colon and ileus with obstruction, which resolved. Although these 3 SAEs were considered possibly related to vedolizumab treatment, a role of progressive aGVHD or complications from previous therapies could not be ruled out based on the data available in these patients' medical records. Overall, 13 SAEs were fatal, of which 7 were infections or sepsis (Table 4).

Table 2
Treatments Other Than Corticosteroids Received by Patients Before or During Vedolizumab Therapy (for Patients in Whom Data Were Available for Extraction)

Treatment	No. of Patients
Budesonide	13
Mycophenolate mofetil	8
Calcineurin inhibitors	10
Extracorporeal photopheresis	5
Ruxolitinib	5
Rapamycin	4
α-1-proteinase inhibitor	2
Rituximab	2
Topical steroid	4
Unspecified anti-TNF agent	1
Methotrexate	1
Tocilizumab	1

TNF, tumor necrosis factor.

Table 3
Response Rates Following Allo-HCT

Response	Patients with a Response at Each Follow-Up, n (%)*						
	2 wk† (n = 18)	4 wk† (n = 9)	8 wk‡ (n = 25)	3 mo‡ (n = 14)	6 mo‡ (n = 19)	12 mo‡ (n = 19)	15 mo‡ (n = 19)
CR	0 (0)	1 (11)	7 (28)	3 (21)	4 (21)	3 (16)	2 (11)
VGPR	2 (11)	0 (0)	6 (24)	1 (7)	0 (0)	1 (5)	0 (0)
PR	7 (39)	5 (56)	3 (12)	0 (0)	0 (0)	0 (0)	0 (0)
No response	8 (44)	2 (22)	3 (12)	3 (21)	1 (5)	0 (0)	0 (0)
Progression	1 (6)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Death	0 (0)	1 (11)	6 (24)	7 (50)	13 (68)	15 (79)	17 (89)
Overall response§	9 (50)	6 (67)	16 (64)	4 (29)	4 (21)	4 (21)	2 (11)

* Percentages are calculated using the total number of patients for whom data were available at each follow-up time (including patients who had died).
† These follow-up times included responses within a range of 1 week either side of the follow-up date; for example, 4 weeks was 3-5 weeks after initiation of vedolizumab.
‡ These follow-up times included responses within a range of 2 weeks either side of the follow-up date; for example, 8 weeks was 6-10 weeks after initiation of vedolizumab.
§ Overall response was defined as PR or better (including PR, VGPR, and CR).

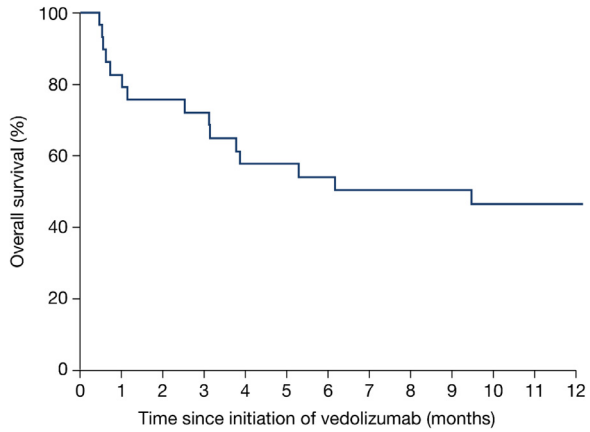

Figure 2. OS up to 12 months after the first dose of vedolizumab. OS at each month is shown from the time of the first dose of vedolizumab (0 months) up to 12 months.

Infections

There were 78 infections recorded in 25 patients (86%), of which 43 were bacterial, 26 were viral, and 9 were fungal; 12 of the infections were SAEs. Of the 43 bacterial infections, 29 (67%) were bacterial sepsis, corresponding to 37% of all infections. The organisms most commonly responsible for bacterial infections were *Staphylococcus* spp (12 of 43; 28%) (Table 5).

Timing of Infections

Of the 78 infections, 74 (95%) were recorded <18 weeks after the last dose of vedolizumab, and 4 (5%) were recorded >18 weeks after the last dose of vedolizumab (Table 5). These 4 infections were 1 *Staphylococcus epidermidis* infection with "other (biopsy)" listed as the location, 1 *Salmonella* infection in the blood (sepsis), 1 *Candida* spp infection in the blood (sepsis), and 1 *Aspergillus* spp infection in the pulmonary system.

Cytomegalovirus Reactivation

Throughout follow-up, 26 viral infections were recorded in 17 patients. Of these, 15 infections were cytomegalovirus (CMV) reactivation in 13 patients. CMV infection involving the pulmonary system, GI tract, or other location was recorded in 1 patient each. The remaining cases of CMV reactivation were asymptomatic viremia. CMV reactivation was considered an SAE in 2 patients. The median interval between vedolizumab initiation and CMV reactivation was 17 days (range, 1 to 91 days).

Table 4
SAEs Experienced Between the Initial Dose of Vedolizumab and the Final Follow-Up

SAE	N (%)
SAEs identified	29 (100)
Infection	12 (41)
Gastrointestinal	4 (14)
Hematologic	4 (14)
Cardiovascular	2 (7)
Central nervous system	2 (7)
Respiratory	2 (7)
Psychological	1 (3)
Multiple organ failure	1 (3)
Renal	1 (3)
SAEs possibly related to vedolizumab treatment*	3 (10)
Fatal SAEs	13 (45)
Fatal infections or sepsis	7 (54)†
Other fatal SAEs‡	6 (46)
Fatal SAEs possibly related to vedolizumab treatment	1 (8)†,§

* Including 1 case of bleeding from the colon and ileus with obstruction, 1 case of CMV colitis, and 1 case of sepsis.
† Percentages calculated as a proportion of the number of fatal SAEs.
‡ The other fatal SAEs were listed as multiple organ failure, acute kidney injury, hemorrhagic shock, gastrointestinal bleeding, depression and weakness, hypotension, and shock-related respiratory failure.
§ One fatal case of sepsis was considered possibly related to vedolizumab treatment; however, the role of active GI aGVHD or its complications could not be ruled out.

GI Infections

In total, 9 infections were explicitly recorded as having a GI origin (6 bacterial, 2 viral, and 1 fungal, in 8 patients) (Table 5). The causative organisms of the 2 viral GI infections were adenovirus and CMV, respectively. There were 2 viral infections that may have had a GI origin in 2 patients with adenovirus and norovirus or rotavirus strains detected in their stool samples (suggestive of viral gastroenteritis), but these were not confirmed. Of the 6 bacterial GI infections, 3 were attributed to *Clostridium difficile*, 1 of which was considered an SAE. The median interval between the initiation of vedolizumab and the diagnosis of GI infection was 31 days (range, 12 to 293 days).

Serious Infections

Of the 12 recorded infections classified as SAEs, 6 were bacterial, 3 were viral, and 3 were fungal. Seven of these infections had a fatal outcome (of which 3 had a GI origin), and 5 resolved. The most common SAE recorded as an infection was sepsis (in 3 patients, all with a fatal outcome). Other SAEs classified as infections occurring in more than 1 patient were CMV

Table 5
Infections Experienced Between the Initial Dose of Vedolizumab and the Final Follow-Up

Infection	N (%)
Viral infections	
Origin of infection	26 (100)
Blood	19 (73)
Gastrointestinal	2 (8)
Pulmonary	2 (8)
Other (DNAemia)	1 (4)
Other (stool sample)	2 (8)
Causative organism	26 (100)
Adenovirus	3 (12)
Cytomegalovirus	15 (58)
Epstein-Barr virus	4 (15)
Influenza	2 (8)
Norovirus/rotavirus	1 (4)
Other (Polyomaviridae)	1 (4)
Fungal infections	
Origin of infection	9 (100)
Blood*	2 (22)*
Gastrointestinal	1 (11)
Pulmonary*	6 (67)*
Causative organism	9 (100)
Aspergillus spp*	4 (44)*
Candida spp*	4 (44)*
Fusarium spp	1 (11)
Bacterial infections	
Origin of infection	43 (100)
Blood*	29 (67)*
Gastrointestinal	6 (14)
Genitourinary	2 (5)
Pulmonary	3 (7)
Skin or mucosa	2 (5)
Other (biopsy)*	1 (2)*
Causative organism	
Clostridium difficile	3 (7)
Enterococcus	3 (7)
Methicillin-resistant *Staphylococcus aureus*	2 (5)
Pseudomonas aeruginosa	2 (5)
Staphylococcus aureus	4 (5)
Other	29 (67)
Bacteroides	1 (2)
Bacteroides fragilis	1 (2)
Bacteroides fragilis beta-lactamase+	1 (2)
Citrobacter braakii	1 (2)
Clostridium ramosum	1 (2)
Corynebacterium jeikeium	1 (2)
Enterobacter cloacae	1 (2)
Enterococcus	3 (7)
Escherichia coli	2 (5)
Klebsiella	3 (7)
Klebsiella pneumoniae	1 (2)
Moraxella	1 (2)
Pneumotosis intestinalis	1 (2)
Proteus vulgaris	1 (2)
Pseudomonas	1 (2)
*Salmonella**	2 (5)*
Staphylococcus aureus + *Klebsiella*	1 (2)
*Staphylococcus epidermidis**	5 (12)*
Staphylococcus haemolyticus	1 (2)
Staphylococcus lugdunesis	1 (2)
Stenotrophomonas maltophilia	1 (2)
Suspected pneumonia (organism unknown)	1 (2)

* Of the 78 infections, 74 (95%) were reported between the first dose of vedolizumab and 18 weeks after the last dose of vedolizumab, and 4 (5%) were reported more than 18 weeks after the last dose of vedolizumab, including 1 *S epidermidis* infection with "other (biopsy)" listed as the location, 1 *Salmonella* infection in the blood (sepsis), 1 *Candida* spp infection in the blood (sepsis), and 1 *Aspergillus* spp infection in the pulmonary system.

colitis (in 2 patients, 1 fatal) and pneumonia (in 2 patients, both fatal). No cases of progressive multifocal leukoencephalopathy were observed during the study.

DISCUSSION

With data on 29 patients extracted retrospectively, this is the largest analysis of clinical outcomes in patients with SR GI aGVHD receiving treatment with vedolizumab reported to date. At 8 weeks after the first dose of vedolizumab, the overall response rate was 64%, with 28% of patients achieving a CR. OS was 54% at 6 months and 47% at 12 months after the first dose of vedolizumab. During the time period evaluated, there were 29 recorded SAEs in 15 patients, 13 of which were fatal. One fatal SAE (grade 4 sepsis) was considered possibly related to vedolizumab treatment; however, the role of active GI aGVHD or its complications could not be ruled out based on the data available in the patient's medical record. Of the 12 recorded infections considered SAEs, 5 were pulmonary in origin (3 of which resulted in death), and 1 originated in the GI tract.

Reported rates of OS in patients with SR aGVHD in the literature are variable, undoubtedly owing to small sample sizes and the heterogeneity of included populations. The weighted mean OS at 6 months across 25 studies identified through a systematic literature review was estimated as 49% for second-line treatment (range, 0% to 86%), although that analysis did not consider the grade of aGVHD or stage of GI involvement [34]. The largest historical study using equine ATG involving 79 patients reported an estimated 6-month OS of 44% [13], and a recent phase III randomized trial comparing ATG with inolimomab reported a 12-month OS of approximately 45% in all patients [35]. The 6-month OS with vedolizumab (54%) was comparable to that seen with other historically used treatments. Previous studies have not detailed the stage of GI involvement at treatment initiation, making it impossible to conclusively determine whether the OS seen with vedolizumab is higher than expected in patients with greater GI involvement. However, considering that most patients in the present study had stage 3 or 4 GI aGVHD at the time of vedolizumab initiation, and that these patients generally have a worse prognosis than those with primary involvement of the skin or liver, vedolizumab may have some clinical benefit in patients with primarily GI involvement.

Smaller case report studies of vedolizumab as second- or later-line therapy in the aGVHD setting have reported mixed results. Fløisand et al [30] reported a series of 6 patients with SR GI aGVHD, 4 of whom received vedolizumab as second-line therapy. Responses were observed in all 6 patients, and there were 4 survivors at a median follow-up of 10 months. Bukauskas et al [27] reported outcomes 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 to 172 days) of follow-up. Similarly, Coltoff et al [28] reported outcomes in 9 patients treated with vedolizumab for SR aGVHD. Most patients experienced decreased abdominal pain and stool output after 4 weeks, suggestive of some clinical benefit; despite this, 8 of the 9 patients died at a median of 22 days (range, 6 to 107 days) of follow-up. The patients had failed 2 to 6 immunosuppressive regimens before the initiation of vedolizumab treatment, and 4 patients had active infection at the initiation of treatment. The latter 2 case series highlight the significant risks associated with patients who fail multiple lines of therapy for SR GI aGVHD. Earlier treatment with vedolizumab may prove more beneficial than delayed treatment, after multiple systemic immunosuppressive agents have been used and infectious complications have developed.

Patients receiving treatment for SR aGVHD are at high risk for infectious complications. In the present study, 29 SAEs were recorded in 15 patients, and 34% of patients experienced an SAE related to an infection; fatal infections were

recorded in 24% of patients. Other studies in patients with SR aGVHD have reported variable rates of infections, including 83% to 100% (34% to 40% fatal) in patients receiving infliximab [15,36,37], 78% to 100% (8% to 50% fatal) in patients receiving alemtuzumab [14,38-42], and 67% (12% fatal) in patients receiving etanercept [43]. However, many of those series did not categorize infections by severity. In patients undergoing allo-HCT, there is a well-known risk of CMV reactivation associated with increased nonrelapse mortality and overall mortality [44]. In the present study, 15 cases of CMV reactivation were recorded in 13 of the 29 patients (45%), 2 of which were considered serious. Rates of CMV reactivation in studies with similar sample sizes reporting these data are variable but generally similar to the rate reported here: 33% with ruxolitinib [17], 38% with alemtuzumab [14], and 50% with pentostatin [12]. Overall, the SAEs recorded during treatment of SR aGVHD with vedolizumab are consistent with those expected in this critically ill patient population receiving additional immunosuppressive therapy. Although the small number of patients reported to Takeda as having received vedolizumab off-label for GI aGVHD means that our results should be interpreted with caution, there is currently no evidence of an increase in fatal SAEs related to infections or CMV reactivation with vedolizumab compared with other published data on off-label treatments for SR aGVHD.

One plausible concern with vedolizumab is the impact of its gut-selective mechanism of action on the risk of GI infection compared with the global immunosuppression seen with other agents used for SR aGVHD. In this study, the number of GI infections in patients treated with vedolizumab appeared low; in all, 9 infections with a GI origin were recorded, accounting for 11.5% of all infections (n = 78). There were no clear patterns in the time to the onset of these infections from vedolizumab initiation (mean, 77 days; range, 12 to 293 days) or in the numbers of infections caused by certain organisms. Taken together, these results indicate that the gut-selective mechanism of action of vedolizumab is unlikely to be associated with an increased risk of GI infection or with an increased susceptibility to infection with specific opportunistic organisms.

One of the main concerns for patients receiving novel immunosuppressive treatments is the loss of the graft-versus-malignancy effect, which potentially could lead to an increased risk of relapse of the primary malignancy [45,46]. In our series, relapse of the primary malignancy occurred in 10% of the patients (3 of 29). In previous studies, Schnitzler et al [41] found that 30% of patients (6 of 20) experienced a relapse of malignancy with alemtuzumab, Nadeau et al [16] reported relapse of malignancy in 24% of patients (5 of 21) treated with a combination of basiliximab and infliximab, and in a Phase I study, Chen et al [20] reported relapse of malignancy in 9% of patients (3 of 34) treated with brentuximab vedotin. A previous evaluation of the influence of other immunosuppressive treatments on recurrence of malignancy indicated that the risk of relapse may increase slightly with long-term immunosuppressive treatment (after approximately 45 months of treatment) [45]. Given that vedolizumab is gut-specific, there is a possibility that it could be less prone to decreasing the systemic graft-versus-malignancy effect; however, larger and longer-term prospective studies are needed to evaluate fully the impact of vedolizumab on disease relapse.

The data reviewed in this study were collected from international transplantation centers reflecting real-world practice, and, although there was heterogeneity in the patient characteristics and methods of assessment, our series likely comprises a representative population of patients with SR GI aGVHD treated with vedolizumab in the second-line setting. Nonetheless, this study has several limitations, largely related to the nature of SR aGVHD and the retrospective collection of data from medical records. First among these limitations is the small sample size, owing to the rarity of SR GI aGVHD. In addition, there was missing information in the medical records that could not be clarified or reconciled, especially for events occurring many months before data abstraction. Although data on treatments received for aGVHD before and during vedolizumab treatment were collected (meaning that observed responses during this time were likely attributable to vedolizumab and/or concomitant therapies), reasons for vedolizumab discontinuation, data on treatments provided after vedolizumab, and vedolizumab serum levels were not collected, making it difficult to assess the effectiveness of vedolizumab with certainty. In addition, data on any improvement or worsening of aGVHD following vedolizumab initiation were not recorded at the individual patient level for each organ, making it impossible to determine whether patients with improvement in GI aGVHD symptoms also had improvement in other organs. A potential for selection bias also should be noted, because there were no prospective eligibility criteria, and also because some centers in which patients received vedolizumab for SR GI aGVHD did not participate in the study. Finally, there have been no prospective trials directly comparing vedolizumab with other treatments, meaning only extrapolative naïve comparisons between vedolizumab and other treatments can be made.

CONCLUSION

Vedolizumab could be a potential treatment option for patients with SR GI aGVHD, based on our observed overall response rate (64% at 8 weeks) and OS (54% at 6 months). The safety profile of vedolizumab for the treatment of SR GI aGVHD is consistent with the expected risks in this seriously ill patient population, with no apparent increase in GI infections in patients treated with this gut-selective immunomodulator. More data on the efficacy and safety of vedolizumab in this setting from prospective trials are needed.

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