Biol Blood Marrow Transplant 23 (2017) 172–175

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Brief Articles

Targeting Integrin α4β7 in Steroid-Refractory Intestinal Graft-versus-Host Disease

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Article history:
Received 18 April 2016
Accepted 13 October 2016

Key Words:
Graft-versus-host disease
Stem cell transplant
Vedolizumab
Gut GVHD
Integrin
Steroid refractory

A B S T R A C T

Steroid refractory acute graft-versus-host-disease of the gut is a serious complication associated with high mortality after allogeneic stem cell transplantation. Treatment options are limited and not predictably effective. We describe the treatment of steroid-refractory acute graft-versus-host-disease with vedolizumab, an antibody directed against integrin α4β7, in 6 patients. All patients responded, and 4 of 6 patients are alive with a median follow-up of 10 months.

INTRODUCTION

Acute graft-versus-host-disease (aGVHD) occurs in up to 50% of patients after allogeneic stem cell transplantation. Grades III to IV GVHD is associated with poor outcome, with a 70% to 90% mortality [1,2]. Severe intestinal involvement is particularly difficult to treat and often leads to prolonged and debilitating illness before death occurs. Treatment of steroid-refractory or steroid-dependent aGVHD is notoriously difficult. Second- and third-line treatments are less than optimally documented, show erratic responses, and imply intensifying systemic immunosuppression with the risk of death due to infectious complications. There is an unmet need for new and more effective therapies with predictable efficacies [1,3].

Vedolizumab, a monoclonal antibody targeting the homing of T cells to the intestinal endothelium through inhibition of binding of integrin α4β7 to mucosal addressin MadCAM-1, is effective in inflammatory bowel disease [4-6]. Because it is selective for receptors in the gut, it has not been associated with progressive multifocal leukencephalopathy, as is the case with monoclonal antibodies also targeting T cell migration to the central nervous system [5].

aGVHD is an immunologically mediated disease in which alloreactive donor T cells are central in the pathogenesis [7]. Expression of α4β7 on donor T cells has been shown to be important in the development of intestinal GVHD in mice [8,9]. Choi et al. [10] have reported that disruption of alloreactive donor T cell trafficking to the target organs significantly reduces GVHD in both MHC fully-mismatched and minor-mismatched allogeneic hematopoietic cell transplantation models. Thus, inhibition of α4β7, which is required for transendothelial migration and access to the intestinal lymphoid system, could be an attractive target for prevention or treatment of aGVHD.

The adhesion molecule MAdCAM-1 belongs to the immunoglobulin superfamily. It is constitutively expressed on high endothelial venules of both mesenteric lymph nodes and Peyer's patches (PPs) and postcapillary venules of the lamina propria. PPs are essential in the development of antihost cytotoxic T cells causing intestinal aGVHD [11]. MAdCAM-1 is the major ligand for α4β7 integrin and is the ligand for L-selectin [12]. The expression level of α4β7 integrin is

Financial disclosure: See Acknowledgments on page 175.
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http://dx.doi.org/10.1016/j.bbmt.2016.10.009
1083-8791/

Table 1
Patient Characteristics

	Patient					
	1	2	3	4	5	6
Diagnosis	AML	AML	NHL	AML	NHL	AML
Sex	Male	Male	Male	Female	Male	Male
Age at transplant, yr	46	58	42	44	50	62
GVHD prophylaxis	CyA + MTX	CyA + MTX	CyA + sirolimus	CyA + MTX	CyA + sirolimus	CyA + MMF
Time to aGVHD, days	36	70	26	30	96	60
Lines of therapy after steroid refractoriness before vedolizumab	2	1	0	0	0	0
Other manifestations			Cytomegalovirus	Renal failure, hepatic failure, and multiorgan GVHD	Cytomegalovirus	
Steroid dose at last follow-up	N/A	N/A	2 mg/kg	1.7 mg/kg	N/A	N/A
Number of vedolizumab doses at last follow-up	9	11	3	1	2	3
Immunosuppression at last follow-up	No	CyA	CyA + steroids	MMF + steroids	CyA	No
Watery stools at last follow-up	No	No	No	No	No	No
Follow-up, mo	12	12	5	1	8	8

AML indicates acute myelogenous leukemia; NHL, non-Hodgkin lymphoma; CyA, Cyclosporin A; MTX, methotrexate; MMF, mycophenolate mofetil; N/A, not applicable.

relatively low on naive T cells and B cells but increased on IgA-secreting plasma cells, memory T cells, and activated gut-homing $CD4^+$ T cells. Furthermore, $\alpha4\beta7$ integrin is expressed on natural killer cells, activated monocytes, macrophages, eosinophils, and dendritic cells [13]. Given the responses seen in inflammatory bowel disease, we used vedolizumab in 6 patients with steroid-refractory intestinal aGVHD.

METHODS

Case Series

The study was approved by the institutional review board, and patients signed informed consent forms for off-label use of the drug. Vedolizumab is currently approved for the treatment of Crohn's disease and ulcerative colitis.

Patient characteristics are provided in Table 1. All patients were categorized as having grade IV intestinal aGVHD, as defined by the Gluckman criteria, with few or no other manifestations of aGVHD. Patients 1 and 2 had been through second- and third-line therapy without improvement of symptoms. Steroid-refractory disease was defined as progressive disease after 3 consecutive days of primary treatment with a calcineurin inhibitor + methylprednisolone 2 mg/kg, a lack of at least a partial response after 7 days of primary treatment with methylprednisolone 2 mg/kg or equivalent, or lack of a complete response after 14 days of primary treatment with methylprednisolone 2 mg/kg or equivalent.

The histologic grading of GVHD was performed using a modification of the system for colonic GVHD described by Lerner et al. [14] as follows:

Grade 1: Isolated apoptotic cells without crypt loss
Grade 2: Loss of isolated crypts without loss of contiguous crypts
Grade 3: Loss of 2 or more contiguous crypts
Grade 4: Extensive crypt loss with mucosal denudation

Following the response observed in patients 1 and 2, patients 3 to 6 received vedolizumab as second-line therapy after steroid failure (Table 1). Previous treatments are described in Table 1. Vedolizumab was delivered as described for inflammatory bowel disease; 300 mg i.v. without premedication on weeks 0, 2 and 6, followed by infusions every 8 weeks on clinical indication and with serum concentration measurements [15]. All patients continued standard immunosuppression with a calcineurin inhibitor or mycophenolate mofetil. Systemic corticosteroids were tapered with response after vedolizumab. Serum levels are defined for patients with Crohn's disease and ulcerative colitis with start and dose escalation trough levels between 10 and 30 mg/L and maintenance levels between 5 and 15 mg/L. Patients requiring long-term treatment not achieving the recommended levels were given infusions every 4 weeks.

RESULTS

Clinical and Histologic Improvement after Treatment with Vedolizumab

All patients exhibited clinical response within 7 to 10 days with decrease in abdominal pain and watery diarrhea. Serial endoscopies were performed and revealed gradual macroscopic and histologic improvement; the stomach and small intestine showed a more rapid improvement than the colon. In the colon, macroscopic improvement was gradual, starting from the distal colon with the cecum and distal ileum exhibiting the slowest speed of repair (Figures 1 and 2).

After 3 doses of vedolizumab, 4 patients were off systemic corticosteroids. Five of 6 patients received oral medication, including immunosuppressants. Concomitant immunosuppressive therapy was cyclosporine or mycophenolate mofetil. There were no or sparse clinical symptoms of intestinal aGVHD, maximum, grade I. Five of 6 patients were discharged from the hospital after the third dose of vedolizumab. Patient 2 initially achieved a complete response after 3 doses of vedolizumab but experienced a relapse of acute myelogenous leukemia and developed grade IV intestinal GVHD after cessation of immunosuppression. He was restarted on vedolizumab with effect, and the GVHD subsided to grades 0 to I within 2 weeks. At last follow-up he was in complete remission of his acute myelogenous leukemia.

Two patients developed complications leading to death. Patient 3 developed skin aGVHD after discharge from the hospital, and high-dose corticosteroids were reinstituted, subsequently complicated by staphylococcal sepsis and acute respiratory distress syndrome, leading to death. Patient 4 already had multiorgan failure with hemodialysis and liver failure before start of vedolizumab treatment. She succumbed to complications of multiorgan failure. An autopsy was declined.

Patients 1 and 2 were receiving continuous treatment with vedolizumab 12 months after start of treatment and displayed no or sparse symptoms of residual intestinal GVHD. Patients 5 and 6 did not require additional treatment after 2 and 3 doses. All 4 patients alive are out of the hospital and attend follow-up in an outpatient clinic with a median follow-up of 10 months.

DISCUSSION

aGVHD remains the major cause of nonrelapse mortality after allogeneic stem cell transplantation and reflects the life-threatening outcome of complex cellular events involving several compartments of the immune system and tissues. aGVHD is an immunologically mediated disease where alloreactive donor T cells are central to the pathogenesis [7]. Inhibiting the T cell–induced inflammatory response could be a promising approach.