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Addition of Infliximab to Standard Acute Graft-versus-Host Disease Prophylaxis following Allogeneic Peripheral Blood Cell Transplantation

Mehdi Hamadani,[1] *Craig C. Hofmeister*,[1] *Buffy Jansak*,[1] *Gary Phillips*,[2] *Patrick Elder*,[1] *William Blum*,[1] *Sam Penza*,[1] *Thomas S. Lin*,[1] *Rebecca Klisovic*,[1] *Guido Marcucci*,[1] *Sherif S. Farag*,[3,4] *Steven M. Devine*[1,4]

[1] Division of Hematology & Oncology, Arthur G. James Cancer Hospital, The Ohio State University Comprehensive Cancer Center, Columbus, OH; [2] Ohio State University, Center for Biostatistics, Columbus, OH; [3] Division of Hematology and Oncology, Indiana University School of Medicine, Indianapolis, IN; and [4] These authors contributed equally to this manuscript

Correspondence and reprint requests: Steven M. Devine, MD, Ohio State University, 320 West 10th Avenue, Columbus, OH 43210 (e-mail: steven.devine@osumc.edu).

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ABSTRACT

Infliximab, a chimeric monoclonal antibody (mAb) against tumor necrosis factor (TNF)-α, has shown activity against steroid refractory acute graft-versus-host disease (aGVHD). We conducted a prospective trial of infliximab for the prophylaxis of aGVHD. Patients older than 20 years undergoing myeloablative allogeneic stem cell transplantation (SCT) for hematologic malignancies were eligible. GVHD prophylaxis consisted of infliximab given 1 day prior to conditioning and then on days 0, +7, +14, +28, and +42, together with standard cyclosporine (CSA) and methotrexate (MTX). Nineteen patients with a median age of 53 years were enrolled. All patients received peripheral blood allografts from matched sibling (n = 14) or unrelated donors (n = 5). Results were compared with a matched historic control group (n = 30) treated contemporaneously at our institution. The cumulative incidences of grades II-IV aGVHD in the infliximab and control groups were 36.8% and 36.6%, respectively ($P = .77$). Rates of chronic GVHD were 78% and 61%, respectively ($P = .22$). Significantly more bacterial and invasive fungal infections were observed in the infliximab group ($P = .01$ and $P = .02$, respectively). Kaplan-Meier estimates of 2-year overall survival (OS) and progression free survival (PFS) for patients receiving infliximab were 42% and 36%, respectively. The corresponding numbers for patients in the control group were 46% and 43%, respectively. The addition of infliximab to standard GVHD prophylaxis did not lower the risk of GVHD and was associated with an increased risk of bacterial and invasive fungal infections.

KEY WORDS

Hematopoitic stem cell transplantation • Allogeneic • Graft-versus-host disease • Steroid refractory • Infliximab • Tumor necrosis factor • Unrelated donor

INTRODUCTION

Acute graft-versus-host disease (aGVHD) is 1 of the most frequent complications after allogeneic hematopoietic stem cell transplantation (HSCT) [1]. Overproduction of tumor necrosis factor-α (TNF-α) is implicated in the pathophysiology of aGVHD through several mechanisms including upregulation of the expression of major histocompatibility complex antigens, endothelial cell and leukocyte adhesion molecules, induction of target tissues apoptosis through TNF-α receptor, activation of macrophages, neutrophils, eosinophils, B cells and T cells, and increased production of additional inflammatory cytokines [2-4]. Elevated serum levels of TNF-α are seen in patients with aGVHD, and may be predictive of the severity of GVHD [5,6].

Infliximab (Remicade, Centocor, Malvern, PA) is a murine-human chimeric IgG1κ monoclonal antibody (mAb) that binds with high affinity to the soluble and transmembrane forms of TNF-α, and inhibits their binding with the cellular receptors [7]. A number of retrospective studies have shown activity of this drug

in the treatment of steroid refractory aGVHD [8-10] generally employing high doses (10 mg/kg/week). Although no prospective clinical trial of infliximab for the prophylaxis of aGVHD has been reported, neutralizing anti-TNF-α mAb administered prior to TBI in murine models have shown significantly delayed mortality and improved body weight in treated mice [11]. We theorized that infliximab may decrease the risk of aGVHD, and therefore conducted a prospective trial to evaluate the efficacy and toxicity of infliximab prophylaxis prior to allogeneic stem cell transplant.

PATIENTS, MATERIALS, AND METHODS

Patient Population

Beginning in April 2004, 19 patients were enrolled at the time of allogeneic transplant for acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), acute lymphoblastic leukemia/lymphoma, non-Hodgkin lymphoma (NHL), Hodgkin's lymphoma (HL), or chronic myelogenous leukemia (CML) in the accelerated phase or blast crisis. Patients undergoing HSCT for CML in the chronic phase or aplastic anemia (AA) were not eligible. CML patients in the chronic phase were excluded because these patients generally have favorable outcomes with standard GVHD prophylaxis (cyclosporine [CsA] + methotrexate [MTX]), and more intense GVHD prophylaxis in this group may increase the risk of disease relapse posttransplantation [12]. Patients with acute leukemia in the first complete remission, MDS with refractory anemia, or refractory anemia with ringed sideroblasts were considered to have low-risk disease. All other patients were placed in the high-risk disease category. Patients with human immunodeficiency virus seropositivity, Karnofsky performance status <60%, and those receiving reduced-intensity conditioning (RIC) were excluded. The study was approved by the Ohio State University institutional review board, and all patients underwent informed consent.

The patients enrolled in this study were compared with an historic control group of 30 patients who had undergone allogeneic HSCT at our center at approximately the same time as the study group (between January 2003 and October 2005), and who had either not consented to the study or were not eligible because of insurance denial. Matching criteria for control group selection included diagnosis, pretransplant disease status, and risk category, age, stem cell source, myeloablative conditioning with TBI or busulfan containing regimen, GVHD prophylaxis, donor type, and degree of HLA match.

HLA Typing and Donor Matching

In patients with sibling donors HLA typing for class I antigens was performed using standard serologic techniques. Typing for Class II alleles (HLA-DRB1) was resolved with sequence-specific oligonucleotide primers for hybridization of amplified DNA, followed by high-resolution typing in all patients and donors. Unrelated donors were matched for HLA-A, -B, and -DRB1 by high-resolution typing.

Treatment Protocol

Infliximab was administered as a 120-minute infusion at 10 mg/kg the day before the conditioning regimen. Five subsequent doses were given on days 0 (after hematopoietic stem cell infusion), +7, +14, +28, and +42. No dose modifications were done for renal or hepatic impairment. All patients received standard prophylaxis of aGVHD with CsA (3 mg/kg/day i.v., commencing on day −1) and short-course MTX (15 mg/m^2 day 1, and 10 mg/m^2 days 3, 6, and 11). Cyclosporine levels were maintained between 150 and 450 ng/mL. From day +100 onward CsA was tapered at the discretion of the treating physician.

Transplantation Procedure and Supportive Care

All patients received myeloablative conditioning regimens using either TBI (1200 cGy) or busulfan (16 mg/kg oral or 12.8 mg/kg i.v.) in combination with other drugs. Donor cells were infused on day 0. Patients were monitored weekly for cytomegalovirus (CMV) reactivation with Digene™ hybrid capture assay. Gancyclovir or foscarnet were used at the discretion of the treating physician for patients with evidence of CMV reactivation. Filgastrim granulocyte-colony stimulating factor (G-CSF) was not routinely administered. CMV negative products were used for CMV seronegative patients. Neutrophil engraftment was defined as the first of 3 successive days after transplantation, with ANC $\geq 0.5 \times 10^9$/L. Platelet engraftment was considered to have occurred on the first of 3 consecutive days with platelet count 20×10^9/L or higher, in the absence of platelet transfusion.

Assessment of GVHD

Staging and grading of aGVHD were scored according to consensus criteria [13]. Biopsies of all involved organs were required to corroborate the clinical diagnosis of aGVHD. Exception was patients with multiorgan aGVHD where liver biopsy was preferred but not required. Liver-only GVHD required biopsy confirmation. Patients were evaluable for chronic GVHD (cGVHD) if engraftment occurred and the patient survived for 100 days posttransplantation. Assessments were made according to previously described criteria [14].

Adverse Events

Adverse events were assessed and recorded after HSCT for an evaluation of safety. Veno-occlusive disease (VOD) was diagnosed and graded according to

Table 1. *Baseline Characteristics of Patients in the Clinical Trial and Their Matched Controls*

	Clinical Trial (N = 19)	Control Group (N = 30)	
	N (%)	N (%)	*P*-Value*
Median age, years (range)	53 (27-64)	43.5 (21-64)	.05
Sex			
Male	13 (68)	20 (67)	.99
Female	6 (32)	10 (33)	
Stem cell source			
PBSC	19 (100)	30 (100)	—
BM	0	0	
Donor source			
HLA-matched related	14 (74)	25 (83)	.49
HLA-mismatched related	0 (0)	1 (3)	
HLA-matched unrelated	4 (21)	2 (7)	
HLA-mismatched unrelated	1 (5)	2 (7)	
Diagnosis			
MDS/AML	11 (58)	21 (70)	.26
Non-Hodgkin lymphoma	4 (21)	3 (10)	
ALL	4 (21)	3 (10)	
HOD	0	3 (10)	
Disease risk			
Standard risk	8	14	.75
High risk	11	16	
Sex match			
Sex matched	9 (47)	16 (54)	.86
Male to female	4 (22)	7 (23)	
Female to male	6 (31)	7 (23)	
ABO matched/mismatched			
Matched	11 (58)	20 (67)	.14
Major mismatch	5 (26)	2 (7)	
Minor mismatch	3 (16)	8 (26)	
Median $CD34^+$ cell dose (10^6 cells/kg recipient wt)	4.95	5.22	.70
Median $CD3^+$ cell dose (10^7 cells/kg recipient wt)	2.94	3.02	.72
G-CSF used			
Yes	12 (63)	13 (43)	.24
No	7 (37)	17 (57)	
Conditioning regimen			
TBI-containing	4 (21)	3 (10)	.41
Bu/Cy	15 (79)	27 (90)	

ALL indicates acute lymphoblastic lymphoma; AML, acute myelogenous leukemia, BM, bone marrow; Bu/Cy, busulphan and cyclophosphamide; G-CSF, granulocyte colony stimulating factor; HOD, Hodgkin lymphoma; MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cells; TBI, total body irradiation.

**P*-values are based on Wilcoxon rank-sum for medians and Fisher's Exact test for categoric data.

McDonald et al. [15] and Bearman [16] criteria, respectively. Infections were documented as "proven" if an organism was isolated or confirmed by serologic, molecular, culture, or histologic evidence, or "suspected" if patients developed fevers and radiologic or clinical evidence of infection without organism identified. Urine and/or serum BK-virus PCR was obtained in all suspected cases of hemorrhagic cystitis. Primary cause of death and treatment related (nonrelapse) mortality (TRM) were defined according to National Marrow Donor Program criteria [17].

Statistical Analysis

The primary efficacy outcome for this study was cumulative incidence of grade II-IV aGVHD within 100 days of allogeneic HSCT. Secondary objectives included incidence of cGVHD, TRM, overall survival (OS), progression free survival (PFS), adverse events, and infectious complications. Competing risk analysis between aGVHD and TRM were used to estimate the cumulative incidence. PFS rates were calculated using death and disease progression as events. Actuarial survival after transplantation was evaluated by the Kaplan-Meier method. Predictors of response were evaluated by logistic regression. Predictors of survival were evaluated by Cox proportional hazards model. Categoric variables and aGVHD incidence between the study group and the historic control group were compared by using the chi-square test or Fisher exact test, as appropriate; continuous variables were compared by using the Mann-Whitney test, and OS and PFS data were analyzed by the log-rank test. Cumulative incidence of aGVHD between infliximab and historical controls was compared using Gray's test. All

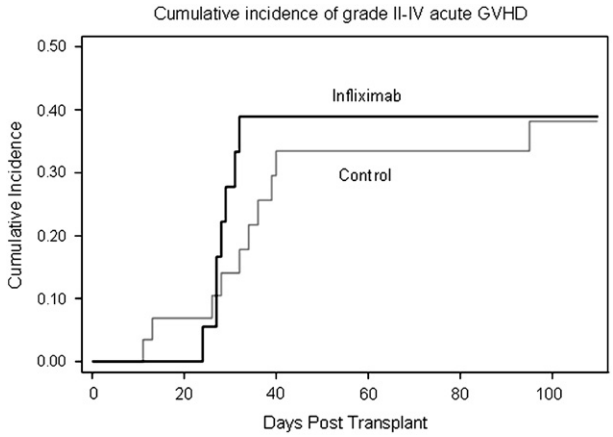

Figure 1. Cumulative incidence of acute grade II-IV GVHD (black and gray curves depict infliximab-treated and control groups, respectively) Gray's test *P*-value = .77.

analyses were run using Stata 10.0 (Stata Corporation, College Station, TX).

RESULTS

Patient and Disease Characteristics

Twenty-four consecutive patients provided informed consent for enrollment in the infliximab group. Five patients did not receive infliximab for GVHD prophylaxis secondary to insurance denial, and are not included in the final analysis. The remaining 19 patients constitute the infliximab group, while 30 matched historical controls were selected. Demographics and transplant characteristics of both groups are summarized in Table 1. Compared to patients receiving infliximab, the control group was slightly younger (median age 43.5 versus 53 years, *P*-value = .05). All patients in the control group received aGVHD prophylaxis with short-course methotrexate and cyclosporine. No patient in either group received a T cell-depleted graft.

Engraftment

There were no engraftment failures in either group. The median time to neutrophil engraftment was 16 days (range: 12-27 days) for patients in the infliximab groups and 14 days (range: 11-23 days) in the control group (*P*-value = .06). Two and 3 patients in the infliximab and control group failed to meet the criteria for platelet engraftment, respectively. The median time to platelet engraftment in the infliximab group (26 days, range: 14-99 days) was significantly longer (*P*-value = .02) compared to the control group (16 days, range: 13-47 days).

Acute GVHD

The cumulative incidence of grade II-IV aGVHD (Figure 1) was 36.8% in the infliximab group (n = 7) and 36.6% in the control group (n = 11) (*P*-value = .77).

Table 2. *Distribution of a GVHD Grades*

Grade of aGVHD	Infliximab Group (%) (N = 19)	Control Group (%) (N = 30)
0	9 (47.3)	10 (33.3)
I	3 (15.7)	9 (30)
II	1 (5.2)	7 (23.3)
III	3 (15.7)	2 (6.6)
IV	3 (15.7)	2 (6.6)

aGVHD indicates acute graft-versus-host disease.

The distribution of aGVHD grades in both groups is presented in Table 2. No difference in the incidence of aGVHD was seen among the 2 groups, across all severity grades (*P*-value = .22). On multivariate logistic regression analysis adjusted for patient age, sex, degree of HLA-compatibility, donor type, and conditioning regimen, no difference in odds of developing aGVHD between the infliximab and control group was found (*P*-value = .94, 95% confidence interval 0.13-3.55). Median time to onset of aGVHD in the infliximab and control groups was 30 and 32 days, respectively (*P*-value = .4). Within the infliximab group no difference (*P*-value = .70) was seen in the median time to the onset of aGVHD in patients conditioned with TBI-containing regimens (29 days) versus those receiving non-TBI-based conditioning (31 days). Distribution of organ involvement was similar between the 2 groups. Among patients undergoing transplantation from sibling donors the rates of grade II-IV aGVHD in the infliximab and control groups were 35.7% (n = 5) and 30.7% (n = 8), respectively (*P*-value = .75), whereas the corresponding rates of grade II-IV aGVHD in recipients of allografts from unrelated donors in the infliximab and control groups were 40% (n = 2) and 75% (n = 3), respectively (*P*-value = .29). Interestingly, subgroup analysis of patients in the infliximab group according to disease risk categories revealed that 7 of 11 patients with high-risk disease (63%) developed grade II-IV aGVHD, whereas none of the 8 patients with standard-risk disease developed grade II-IV aGVHD (*P*-value = .004). Five of 16 patients with high-risk disease in the control group (31%) developed grade II-IV aGVHD. This was not significantly different from rates seen in high risk patients in the infliximab group (*P*-value = .09). However, among patients with standard-risk disease infliximab produced significantly better control of grade II-IV aGVHD (0%) compared to the control group (42%) (*P*-value = .02).

Chronic GVHD

Fourteen patients in the infliximab group and 26 in the control group were evaluable for cGVHD. In patients receiving infliximab prophylaxis, the incidence of cGVHD was 78% (n = 11), compared to 61% (n = 16) in the control group (*P*-value = .22).

Table 3. *Infections in Patients Receiving Infliximab Prophylaxis and Control Group*

Type of Infections	Clinical Trial No. of Patients (%)	Control Group No. of Patients (%)
Bacterial		
Gram-positive		
Staphylococcus aureus	6 (31)	3 (10)
***Staphylococcus* (not aureus)**	11 (58)	11 (37)
Enterococcus	3 (16)	5 (16)
Clostridium difficile	5 (26)	7 (23)
Other	3 (16)	—
Gram-negative	8 (42)	10 (33)
Fungal		
Candida glabrata	2 (10)	0
***Candida* spp**	1 (5)	0
***Aspergillus* spp**	2 (10)	1 (3)
Viral		
Cytomegalovirus	13 (68)	18 (60)
BK-virus	4 (21)	3 (10)
Adenovirus	—	—
Epstein-Barr virus	—	1 (3)
Others	1 (5)	1 (3)

Nine patients in the infliximab group and 11 in the control group had extensive cGVHD (*P*-value = .44).

Toxicity and Infections

Four patients did not receive all of the planned 6 doses of infliximab. Reasons of discontinuation included: development of grade III-IV aGVHD while still receiving infliximab prophylaxis (n = 2), disease progression in the central nervous system in a patient with Burkitt lymphoma (n = 1) and overwhelming sepsis (n = 1). No allergic or infusion-related adverse events were attributed to infliximab. Similarly, no neurologic or cardiac complications attributable to infliximab developed. No cases of posttransplant lymphoproliferative disease, second malignancies, tuberculosis, or atypical mycobacterium developed. Noninfectious complications possibly related to infliximab included: nausea/vomiting (n = 1), fatigue (n = 1), diarrhea (n = 1), night sweats (n = 1), pulmonary fibrosis (n = 1), acute respiratory distress syndrome (n = 2), transient renal insufficiency (n = 2), shortness of breath (n = 1), pleural effusion (n = 1) and gastric bleeding (n = 1).

Infectious complications were frequent. Table 3 summarizes proved infections among patients in the infliximab and control group. Five patients developed invasive fungal infections including; invasive pulmonary aspergillosis (n = 2), candidemia (n = 1), pulmonary candidiasis (n = 1) and candida urinary tract infection (n = 1) in the infliximab group. Compared to the control group, invasive fungal infections were significantly more frequent in the infliximab group (*P*-value = .03). Viral infections in the infliximab group included CMV reactivation (n = 13), BK virus-associated hemorrhagic cystitis (n = 4), and varicella zoster virus reactivation (n = 1). One patient developed CMV pneumonitis. In contrast in the control group, 18 patients developed CMV reactivation and 3 had BK virus-associated hemorrhagic cystitis. In addition, 1 episode each of influenza A and EBV reactivation was seen in the control group. No significant difference between the 2 groups was present in terms of viral infections (*P*-value = .90). In the infliximab group, 18 patients (95%) developed a total of 40 bacterial infectious events (including 26 episodes of bacteremias, 3 urinary tract infections, 7 episodes of *Clostridium difficile* colitis, and 4 respiratory tract infections). In the control group, 19 patients (63%) developed a total of 39 bacterial infections (*P*-value = .01).

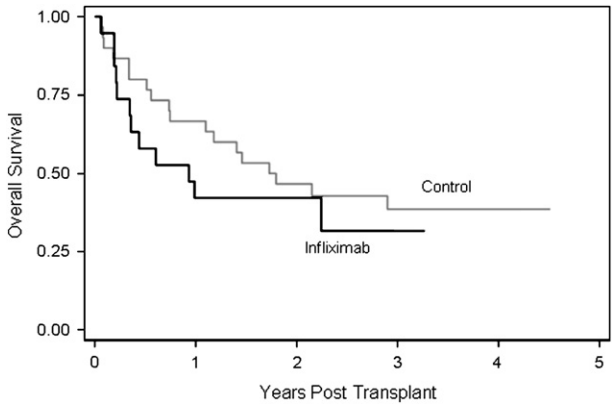

Figure 2. Kaplan-Meier estimates of OS (black and gray curves depict infliximab-treated and control groups, respectively) Log-rank *P*-value = .43.

Outcomes

Seven patients in the infliximab group are alive at a median follow-up of 34 months (range: 21-42 months). All surviving patients have cGVHD (6 patients have extensive cGVHD), and display no evidence of disease progression. Twelve of 19 enrolled patients died. Causes of death included disease relapse (n = 6), GVHD (n = 3), pulmonary invasive fungal infections in patients with GVHD (n = 2) and sepsis with multiorgan failure (n = 1). The Kaplan-Meier estimates of OS at 2 years after transplantation were 42% in the infliximab group and 46% in the control group (*P*-value = .49) (Figure 2). Similarly, estimates of the 2-year PFS between the 2 groups were 36% and 43%, respectively (*P*-value = .50) (Figure 3). Six patients in the infliximab group experienced disease relapse (31%) compared to 10 patients (33%) in the control group (P-value = .89). No significant difference in the day 100 TRM rates between infliximab (21%) and control (13%) groups was seen (*P*-value = .47). Two-year TRM rates were 31% (n = 6) and 26% (n = 8) in the infliximab and control groups, respectively (*P*-value = .76).

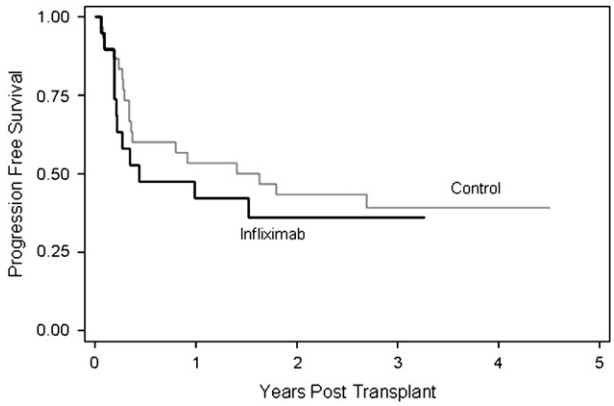

Figure 3. Kaplan-Meier estimates of PFS (black and gray curves depict infliximab-treated and control groups, respectively) Log-rank *P*-value = .50.

DISCUSSION

Despite recent advances, GVHD remains a significant barrier toward broader and safer application of allogeneic HSCT. Effective prophylaxis of aGVHD remains crucial for improving allogeneic transplant outcomes. The role of TNF-α in the pathogenesis of aGVHD is supported by successful prevention of murine GVHD by neutralizing polyclonal TNF-α antibody before TBI and allografting [3,11]. Although infliximab has shown activity in steroid refractory aGVHD [8-10,18,19], it has not been formally evaluated as a prophylactic agent for aGVHD.

Holler et al. [20] reported delayed onset and severity of aGVHD disease (especially in patients receiving TBI-based conditioning) with MAK 195F, a murine monoclonal antibody neutralizing human TNF-α (not available in United States) compared to historic controls. In contrast, we did not detect any significant difference in the incidence, severity, or time to onset of aGVHD following incorporation of infliximab into a standard GVHD prophylaxis regimen. Standard aGVHD prophylaxis used in both studies was identical (CsA and MTX). These paradoxical GVHD-related outcomes reported in our study compared to those reported by Holler et al. might be secondary to unknown biologic differences between these 2 TNF-α blocking agents. Patient selection may have a role. Interestingly, the MAK 195F trial included younger patients (median age, 45.2 years) with matched sibling donors and the majority of enrolled patients had CML in the first chronic phase. In contrast, our patients were older, the majority had high-risk disease (n = 11), and included those receiving unrelated donor grafts.

TNF-α has shown no protective effects on development of cGVHD in murine models [3]. No statistically significant impact of TNF-α antibody on cGVHD was seen in the MAK 195F study [20]. In our trial, a statistically nonsignificant trend toward increased GVHD was seen with infliximab use. Increased incidence of cGVHD in 90% of patients receiving infliximab for steroid refractory aGVHD has been reported previously [8].

Infliximab use in our study was associated with significantly delayed engraftment of platelets and a trend toward delayed neutrophil engraftment as well. TNF-α has been shown to strongly augment interleukin-3-induced short-term proliferation of human $CD34^+$ hematopoietic progenitor cells [21]. Abrogation of this effect might lead to delayed engraftment seen in our study. Delayed neutrophil and platelet engraftment was also apparent in the MAK 195F study, especially in cohorts receiving higher doses of TNF- antibody [20]. There has been an increase in infectious complications with the use of infliximab in patients with steroid refractory aGVHD [8,18,19]. Marty et al. [22] reported a significantly increased risk of invasive fungal infections with infliximab (45%) in patients with steroid refractory GVHD compared to those not exposed to the drug (12%). However, patients in these studies with steroid refractory GVHD were profoundly immunocompromised. Nevertheless, infliximab use in our study, as prophylaxis of aGVHD, was associated with a significantly increased incidence of fungal and bacterial infections.

The dose of infliximab employed in our study for GVHD prophylaxis (10 mg/kg) was selected based on the dose used in the majority of the studies reporting infliximab's efficacy in steroid-refractory aGVHD, and is higher compared to the infliximab dose (5 mg/kg) recommended for rheumatologic indications [8,9,18,19,23-26]. We did not perform any pharmacokinetic sampling, and therefore it is possible that other dosing schemes might be more effective in this setting. The frequent infectious complications seen in our study might be secondary to the dose and administration schedule of infliximab; however, such infectious events are well documented, even with standard (5 mg/kg) infliximab dosing schedules [23,25,27]. This study has several limitations. Prospectively enrolled patients who received infliximab for aGVHD prophylaxis were compared to matched historic controls previously treated in our institution. Although the control group was well matched, this type of analysis is confounded by inherent selection bias. Nevertheless, important conclusions can be drawn. Infliximab use did not produce a significant improvement in the cumulative incidence of aGVHD, may have delayed platelet engraftment, and was associated with frequent infectious complications. Infliximab is unlikely to make a major impact in controlling and preventing aGVHD following myeloablative conditioning at least in patients with high-risk hematologic malignancies.

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