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Upper Gastrointestinal Bleeding During the First Month After Renal Transplantation in the Mycophenolate Mofetil Era

M.R. Ardalan, J. Etemadi, M.H. Somi, A. Ghafari, and M. Ghojazadeh

ABSTRACT

Upper gastrointestinal (GI) bleeding remains a significant cause of mortality and morbidity among renal transplant recipients. We retrospectively analyzed the records of patients who received renal transplantations between January 2001 and July 2007 using mycophenolate mofetil (MMF) in their immunosuppressive regimens. The following data were recorded for those subjects with upper GI bleeding during the first month after transplantation (group B, cases): age, sex, acute rejection episodes, pretransplant upper GI endoscopic findings, *Helicobacter* positivity, and cytomegalovirus (CMV) seropositivity. The same parameters were studied among a group of patients, who did not have a history of upper GI bleeding (group A, controls). A statistical analysis was performed to ascertain potential risk factors. Among 523 patients (311 females, 212 males) of age range 7 to 58 years, 27 (5.2%) had upper GI bleeding: 13 males and 14 females of mean age 44 ± 12 years. The most frequent endoscopic finding was erosive gastritis (n = 13; 48.1%) followed by duodenal ulcers. Binary logistic regression analysis comparing the 2 groups showed that acute rejection episodes ($P = .015$) and active CMV infection ($P = .046$) were the most prominent risk factors for upper GI bleeding during the first month after renal transplantation.

RENAL TRANSPLANTATION is the most effective treatment for end-stage renal disease. Its effectiveness has been improved with new immunosuppressive regimens. Among the most prevalent adverse events among transplant recipients are gastrointestinal (GI) complications, which not only affect the quality of life but also may be life-threatening. They range from nausea, vomiting, diarrhea, and GI bleeding to perforation.[1] The reported incidence of posttransplant upper GI bleeding ranges from 5% to 12%.[2] Multiple risk factors may contribute to GI complications: stress of surgery, nonsteroidal anti-inflammatory drugs, steroids, and impaired native gastroduodenal cytoprotection due to immunosuppressive drugs.[3,4] Previous histories of gastroduodenal ulcer,[5] cytomegalovirus (CMV) infection,[6] *Helicobacter pylori*,[7,8] or erosive gastritis and duodenitis are additional proposed risk factors.[8,9] In this study, we retrospectively investigated the incidence and presumptive risk factors for upper GI bleeding during the first month after renal transplantation among a group of patients who had mycophenolate mofetil (MMF) as part of their immunosuppressive regimens.

MATERIALS AND METHODS

We retrospectively analyzed the records of patients who received renal transplantations in our centers between January 2001 and July 2007. We only included patients who had MMF in their immunosuppressive regimens. For all recipients immunosuppression was routinely started with corticosteroids, cyclosporine, and MMF. The steroid regimen began with intravenous methylprednisolone (500–1000 mg for 3 days) followed by tapering dosages of oral prednisolone. Cyclosporine (CsA) was started at 6 to 7 mg/kg/d and then adjusted based on blood trough levels. MMF was prescribed at 2000 mg/d and adjusted based on white blood cell counts and clinical conditions. H2 receptor blockers were routinely started in the early postoperative period. An acute rejection episode (ARE) was defined as the need for treatment with high-dose methylprednisolone (500–1000 mg for 3 days) with or

From the Department of Nephrology (M.R.A., J.E.), Liver and Gastrointestinal Disease Research Center (M.H.S.), and Faculty of Medicine (M.G.), Tabriz University of Medical Sciences, Tabriz, Iran, and Department of Nephrology, Urmia University of Medical sciences, Urmia, Iran (A.G.).

Address reprint requests to Mohammad Reza Ardalan, MD, Department of Nephrology, Tabriz University of Medical Sciences, Tabriz, Iran. E-mail: ardalan34@yahoo.com

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without antithymocyte globulin (ATG). Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation. Acute CMV infection was defined as a positive anti-CMV IgM antibody test.

Pretransplant upper GI endoscopy was part of our routine workup. After transplantation it was performed mainly because of hematemesis, melena, epigastric pain, or indications noted by the GI consultant. Upper GI bleeding was defined as the presence of an active bleeding lesion upon upper GI endoscopy.

We retrospectively studied the following parameters among patients with documented upper GI bleeding during the first month after transplantation (group B): age, sex, treated with high-dose corticosteroid, and/or ATG, DGF, or a history of pretransplant abnormal upper GI endoscopic findings of erosive gastritis, gastric ulcer, duodenal ulcer, bulbar erosion, *Helicobacter* positivity, or CMV seropositivity. The same parameters were studied among a group of patients who did not experience upper GI bleeding during the first month after transplantation (group A). This group was allocated after defining the subjects with upper GI bleeding. We registered patients who received renal transplantation in the first week of each month to gather a group of controls at least 3 times greater than our cases. Statistical analysis was performed using SPSS version 13 software.

RESULTS

In a 7-year period, 523 patients including 311 females and 212 males of age range 7 to 58 years received renal transplantations. Eighteen received cadaveric (3.44%) and 505 (96.55%) living donor allografts. Endoscopically proven upper GI bleeding occurred in 27 (5.2%) during the first month after transplantation (group B): 14 women and 13 men of overall mean age of 44 ± 12 years. Among these subjects the most frequent endoscopic finding was erosive gastritis (n = 13; 48.1%) followed by duodenal ulcer (n = 10; 37%) and gastric ulcer (n = 4; 14.8%). One of our patients with an active duodenal ulcer died during the first month after transplantation.

Defined risk factors for upper GI bleeding were studied in 89 renal transplant patients (34 women, 55 men) without GI bleeding who were assigned to be the control group (group A). After excluding patients with missing data from both groups A and B, a logistic regression analysis was performed to determine meaningful risk factors for upper GI bleeding. After 9 patients were excluded because of incomplete data (5 cases, 4 controls), we analyzed data from 107 patients. There were 85 patients (32 females, 53 males) in group A and 22 (13 females, 9 males) in group B. The patients in group B were older than those in group A (Mann-Whitney test; $P = .015$). Although men tended to show a lower rate of posttransplant GI bleeding (14.5% vs 28.9% in female patients), the trend was insignificant ($P = .069$). Moreover, patients with acute allograft rejection episodes, positive IgM antibody seroreactivity to CMV, and DGF displayed greater rates of posttransplant GI bleeding (Table 1).

Table 1. Characteristics of Patients With and Without GI Bleeding

	Group A (n = 85)	Group B (n = 22)	*P*
Age (y)	37.4 ± 12.8	45.0 ± 11.5	.015*
Male sex	53 (62.4)	9 (40.9)	.069†
CMV IgG seroreactivity	84 (98.8)	18 (81.8)	.006‡
CMV IgM seroreactivity	4 (4.7)	6 (27.3)	.005‡
ARE treated with MP	16 (18.8)	13 (59.1)	.0002†
ARE treated with MP + ATG	15 (17.6)	8 (36.4)	.057†
DGF	4 (4.7)	5 (22.7)	.017‡
Significant endoscopic findings	50 (58.8)	13 (59.1)	.982†
Helicobacter pylori positivity	43 (50.6)	7 (31.8)	.116†

Data are presented as means ± SDs or numbers (percentages) when appropriate. MP, methylprednisolone; ATG, antithymocyte globulin.
*Mann-Whitney *U* test.
†Chi-square test.
‡Fisher exact test.

A binary logistic regression analysis was performed using age, sex, CMV seroreactivity, ARE treated with methylprednisolone with or without ATG, and DGF as covariates to explore independent factors associated with posttransplant GI bleeding. ARE and CMV IgM seroreactivity were significant risk factors associated with an increased risk for posttransplant GI bleeding (Table 2).

DISCUSSION

In this retrospective study, we observed that ARE and active CMV infection were the most prominent risk factors for upper GI bleeding during the first month after renal transplantation. The incidence of upper GI bleeding in our study was compatible with that reported in previous studies.[2,10] MMF has been reported to be a cause of GI complications.[1] We did not observe an increased incidence of upper GI bleeding among our patients compared with previous reports of subjects who received non-MMF regimens.[3]

CMV is one of the most important posttransplant pathogens. It can cause GI tract ulceration, erosion, and mucosal hemorrhage.[6] We supposed that in our study subjects with active CMV infections had more stressful conditions and were more susceptible to GI bleeding. Meech et al[10] reported that upper GI complications (principally hemorrhage) occurred among 4.1% of renal transplant recipients and AREs were a major risk factor for bleeding. High-dose corticosteroids are a major component of ARE treatment. A strong association has been noted between intravenous high-dose methylprednisolone pulses and the development of peptic ulcers.[11] In our study, the majority of patients with ARE only received high-dose methylprednisolone, a group that showed a meaningful statistical result. Despite advances in immunosuppressive therapy, upper GI bleeding remains a significant cause of mortality and morbidity among renal transplant recipients. GI bleeding can occur any time after renal transplantation; however, the high probability of risk factors during the early period increases the risk of bleeding in this period.

In conclusion, we need more effective antipeptic ulcer prophylaxis covering the first few months after transplanta-

Table 2. Binary Logistic Regression Model

Covariate	Significance (*P*)
Age	.119
Sex	.143
CMV IgM	.046
CMV IgG	.183
ARE treated with MP	.015
ARE treated with MP + ATG	.098
DGF	.109

Hosmer-Lemeshow goodness-of-fit test chi-square = 4.761, df = 8, $P = 0.783$; Nagelkerke $R^2 = .445$. MP, methylprednisolone; ATG, antithymocyte globulin.

tion and must be aware of the greater possibility of GI bleeding during AREs.

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