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The outcomes of mycophenolate mofetil-related gastrointestinal mucosal injury in kidney transplant recipients

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Objectives : Mycophenolate mofetil(MMF) causes gastrointestinal adverse effects in 45% of kidney transplant recipients, as enterocytes are partially dependent on de-novo pathway of purine synthesis. The study aims to describe the outcomes of immunosuppression modification in symptomatic kidney transplant recipients having histopathological evidence of MMF-related toxicity.
Methods : A retrospective observational study from January 2009 to December 2018 at Sanjay Gandhi Postgraduate Institute, Lucknow. All cases that had evidence of MMF-associated histopathological changes and underwent immunosuppression modification were included and studied.
Results : Among 122 recipients who underwent endoscopic biopsy, MMF-associated histopathological changes were observed in 102(83.6%) cases. The indication of endoscopy was persistent or chronic diarrhea in 83.3%(n=85), and non-diarrheal causes in 16.7%(n=17) cases. The associated features were anemia(45.1%,n=46), weight loss(37.3%,n=38) and rectal bleed(6.9%,n=7). Mean duration was 58.15±52.34(1-274) months post-transplant. Mean creatinine was 1.84±0.91mg/dl. All patients were on a triple immunosuppressive regimen, with either mycophenolate mofetil(79.4%,n=81) or enteric-coated mycophenolate sodium(20.6%,n=21). The comorbidities included diabetes(40.2%,n=41), tuberculosis(26.5%,n=27), CMV infection(37.3%,n=38), prior antirejection therapy(33.3%,n=34), and chronic renal allograft injury(46.1%,n=47). 2 cases had coexisting post-transplant lymphoproliferative disorder. Despite conservative management and treatment of associated conditions, 61(59.8%) patients with persistent symptoms required immunosuppressive drug modification. MMF was changed to enteric-coated mycophenolate sodium(ECMPS) in 20(32.8%), Azathioprine in 25(41.0%), and mTOR inhibitors in 4(6.6%) cases, while MMF/ECMPS was discontinued completely in 12(19.7%) cases. Response was seen in 52(85.2%) patients. However, 18(29.5%) patients developed biopsy-proven rejection on drug modification. MMF was reintroduced in 6 patients, but 2 patients had diarrhea recurrence. During a mean follow-up period of 57.5 months, 18 patients had CRAI including 8 graft losses, 17 patients died, and 19 patients were lost to follow-up.
Conclusions : GI toxicity related to mycophenolate therapy is fairly prevalent in kidney transplant recipients. The severe symptomatic cases require immunosuppression modification, which can result in an increased risk of rejection and de-novo DSA formation.

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Table 1: Demographic profile and baseline clinical characteristics			
	Total (n=102)	**Immunosuppression modified (n=61)**	**Immunosuppression not modified (n=41)**
Gender	85 males and 17 females	54 males and 7 females	31 males and 10 females
Mean age (years)	43.86 ± 14.49 (17-75)	43.15 ± 14.08 (17-72)	44.90 ± 15.19 (19-75)
Mean duration post-transplantation (months)	58.15 ± 52.34 (1-274)	54.67 ± 49.12 (1-274)	63.32 ± 57.02 (1-218)
Mean creatinine (mg/dl)	1.84 ± 0.91	1.76 ± 0.77	1.96 ± 1.08
Immunosuppression drugs			
• Mycophenolate mofetil	85 (83.3%)	53 (86.9%)	32 (78.0%)
• Mycophenolate sodium	17 (16.7%)	8 (13.1%)	9 (21.9%)
• Tacrolimus	83 (81.4%)	50 (82.0%)	33 (80.5%)
• Cyclosporine	19 (18.6%)	11 (18.0%)	8 (19.5%)
• Steroid	102 (100%)	61 (100%)	41 (100%)
Comorbidities			
• Diabetes mellitus	41 (40.2%)	25 (41.0%)	16 (39.0%)
• Tuberculosis	27 (26.5%)	15 (24.6%)	12 (29.3%)
• CMV infection	38 (37.3%)	27 (44.3%)	11 (26.8%)
• Prior antirejection therapy	34 (33.3%)	19 (31.1%)	15 (36.6%)
• Chronic renal allograft injury	47 (46.1%)	26 (42.6%)	21 (51.2%)
Associated features			
• Anemia	22 (21.6%)	14 (22.9%)	8 (19.5%)
• Weight loss	38 (37.3%)	22 (36.1%)	16 (39.0%)
• Rectal bleed	7 (6.9%)	6 (9.8%)	1 (2.4%)

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Table 2: Immunosuppression modulation in MMF related histopathological GI toxicity			
	(n)	**Response**	**Biopsy proven rejection**
MMF changed to ECMPS	20	19 (95.0%)	4 (20.0%)
MMF/ECMPS changed to AZA	25	20 (80.0%)	9 (36.0%)
MMF/ECMPS changed to mTORi	4	4 (100.0%)	2 (50.0%)
MMF/ECMPS discontinued	12	9 (75.0%)	3 (25.0%)
	61	**52 (85.2%)**	**18 (29.5%)**